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THE PROBLEM OF THE NEONATAL UMBILICUS AND ITS RELATION TO THE INCIDENCE OF SEPSIS IN A MATERNITY UNIT

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A NUMBER of observers have recently established that the neonatal umbilical stump may play an important part in the spread of staphylococcal infection in maternity units (Gillespie, Simpson and Tozer, 1958; Fairchild, Graber, Vogel and Ingersoll, 1958). Although the epidemiology of such infections is obviously complex, involving many other factors than the umbilicus, it is reasonable to consider that the control of bacterial colonization of the umbilical stump should be one of the measures taken to reduce the incidence of neonatal and maternal sepsis due to staphylococci.

The investigations reported here were carried out during the period April, 1957 to August, 1959 and were designed to determine:

(1) The time and incidence of colonization of the umbilical stump by *Staphylococcus aureus*.

(2) The effect of various methods of stump treatment on the incidence of bacterial colonization.

(3) The relationship between colonization of the umbilical stump and staphylococcal sepsis in the maternity ward.

MATERIALS AND METHODS

The Maternity Unit

The maternity unit is accommodated in one of the hospital blocks and comprises two identical wards, one above the other. Although each ward, with the exception of the Superintendent Midwife, the medical officers and the medical students, is separately staffed, there is considerable mixing of the two staffs. Each ward consists of two parts which are separated by a short corridor into which open the stairs, lifts, nursery and ward kitchen. One part contains four single cubicles, which are used for patients with severe pre-eclampsia, infections and complications of early pregnancy, and an open antenatal ward of six beds, which occasionally accommodates a puerperal mother.

The other part of each ward is open and accommodates ten delivered mothers, and adjacent to it is the labour ward and other offices. The average distance between bedsides is 4 feet 6 inches (minimum 2 feet 6 inches, maximum 6 feet), which gives an average floor area of 105 square feet per patient.

During the daytime the babies remain in the ward beside the mothers' beds. The babies only stay in the nursery at night. The floor area of the nurseries is 280 square feet and the number of babies accommodated at one time is 12 to 18. The upper maternity ward has two additional smaller nurseries, which are used for premature babies and the isolation of infected infants. More recently the policy has been to isolate mother and baby together in one of the cubicles if either or both are affected.

There are approximately 700 deliveries each year and the approximate length of stay for each patient is 10 to 12 days.

Recording of Sepsis

A history card was kept for each baby born in the ward and continued in the follow-up clinic. The nursing staff also kept a day-book in which weights, feeds, the state of the umbilicus, the incidence of sepsis and any other abnormalities were recorded.

A purely arbitrary distinction was made between major and minor sepsis in the babies. The criteria for minor sepsis was no more than two of the following: paronychia, a watering eye or one with purulent discharge but without oedema of the lids, slight serous or blood-stained discharge from the umbilicus more than three days after separation of the cord with or without a small polyp, and less than six pustules on the skin. Cases recorded as major sepsis had more than two of these lesions, or lesions for which treatment by antibiotics or by surgical drainage was considered necessary. Urticaria neonatorum, sebaceous spots, desquamation and cracks in the flexures were excluded unless obviously secondarily infected.

Seventy-five per cent of the infants were followed up for more than three weeks and only 10 per cent were never seen again after discharge from hospital. It was found that it was rare for severe sepsis to develop after the infant had left hospital and particularly if it had not shown some evidence of infection during its stay in the ward. All the staphylococcal lesions occurring in the mothers from the time of delivery until their postnatal visit six weeks after delivery have been recorded. As over 90 per cent of the patients attended the postnatal clinic it is felt that the observations recorded fairly represent the incidence of maternal and neonatal sepsis, particularly as a close liaison was established with the Casualty Department and the surgeons, so that patients treated by them could be included.

Bacteriological Investigations

Umbilical swabs and swabs from septic lesions were cultured aerobically on horse blood agar plates. Coagulase tests were carried out on all staphylococci isolated and their sensitivity to penicillin, streptomycin, erythromycin, chloramphenicol and tetracycline was determined by a standard disc technique. Cultures were recorded as positive only when coagulase-positive staphylococci were grown. No attempt at a quantitative assessment of the colonization was made, since if any growth occurred at all it was usually profuse. Continuous phage typing was not done. Occasional batches of organisms isolated over a short period of time were phage typed; as the findings do not contribute to the objectives of the investigation the results are not recorded here.

Treatment of the Umbilical Stump

The effects on the incidence of staphylococcal colonization of ten different techniques of treatment of the umbilical stump were observed. The details of the techniques used are presented in Table I. It will be seen that there were five consecutive series of investigations during the period April, 1957 to August, 1958 and that in each a comparison of three techniques of treatment (A, B and C) was made. In each series infants at birth were allotted by rotation to either Group A, B or C. In the Series 1–4 the groups were made up as follows:

(A) Control group: standard non-occlusive spirit technique.

(B) Antibiotic or antiseptic non-occlusive technique.

TABLE I

Details of the Techniques Used in the Treatment of the Umbilical Stump

Series	Period	Group	Treatment	No. of Cases
1st	April–May, 1957	A	Daily swabbing with spirit	37
		B	Application of 1 per cent aureomycin cream daily	29
		C	Sterile gauze dressing applied daily	27
2nd	May–September, 1957	A	Daily swabbing with spirit	71
		B	Daily spray with Polybactrin	67
		C	Tube gauze dressing applied and left after initial spraying with Polybactrin	64
3rd	September–December, 1957	A	Daily swabbing with spirit	62
		B	Daily paint with triple dye	48
		C	Enclosed in keyhole dressing with cord powder and covered with binder; dressing not disturbed	53
4th	December, 1957–April, 1958	A	Daily swabbing with spirit	92
		B	Daily application with 1 per cent Hibitane cream	83
		C	Enclosed in keyhole dressing with cord powder and covered with binder; dressing not disturbed	79
5th	April–August, 1958	A	Cord ligated with two elastic bands, daily spirit swabbing	65
		B	Cord ligated with two rubber bands enclosed in keyhole dressing with cord powder and covered with binder; dressing not disturbed	69
		C	Cord enclosed in keyhole dressing with cord powder and covered with binder; dressing not disturbed	62

(C) Occlusive technique with or without antibiotics.

In Series 5, Groups A and B, the technique of ligating the umbilical stump was changed. Two sterile, narrow, elastic bands were used instead of the sterile, woven cotton tape, which had been used in all other groups of the five series. In all cases an umbilical stump 1½–2 inches long was left. Treatment was continued in every case for 7 days and on the 7th day a swab was taken.

RESULTS

A. THE TIME AND INCIDENCE OF COLONIZATION OF THE UMBILICAL STUMP BY *Staphylococcus aureus*

Umbilical swabs were taken from 12 randomly selected, apparently normal infants (6 from each ward), within 24 hours of birth and on four to six of the subsequent 10 days. The umbilicus was treated in each case by the standard non-occlusive spirit technique (as in Table I). There was prompt colonization by coagulase-positive staphylococci in 10 of 11 infants, from whom swabs were received within 24 hours of birth. There was colonization of the umbilical stumps of all 12 babies by *Staph. aureus* within 48 hours of birth and none of the subsequent swabs were sterile.

B. THE EFFECTS OF VARIOUS TECHNIQUES OF TREATMENT ON STAPHYLOCOCCAL COLONIZATION OF THE UMBILICAL STUMP

The findings in both wards were virtually identical and the results from the unit as a whole are presented in Figure 1. Statistical analysis of these results shows that, compared with the control group (Groups A in Table I) there was a significant reduction ($P<0{\cdot}001$) in the staphylococcal colonization of cord stumps treated daily with polybactrin, triple dye or chlorhexidine, or those enclosed with cord power (N.F.) in a keyhole dressing, secured with a binder and left covered for 7 days. The reduction

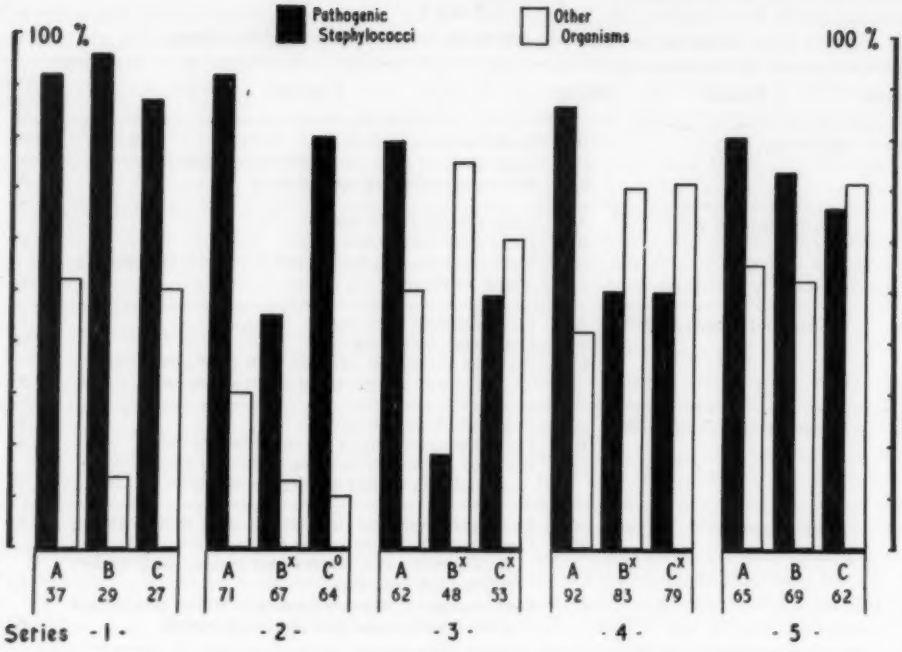

FIG. 1

The effects of various techniques of treatment on the staphylococcal colonization of the umbilical stump. The number of cases in each group is indicated beneath the group letter in each of the series. The number of cases in which pathogenic staphylococci and other organisms were isolated from swabs taken from the umbilical stump on the 7th day, are expressed as a percentage of the total number of cases in each group.

See Table I for the details of treatment.

[x] The reduction in staphylococcal colonization is statistically significant $P<0{\cdot}001$.

[o] The reduction in staphylococcal colonization is probably significant $P<0{\cdot}05$.

of bacterial colonization with tube gauze dressing after an initial application of polybactrin was less convincing ($P<0{\cdot}05$).

C. The Relationship Between Bacterial Colonization of the Umbilicus and the Infant Sepsis Rate

(1) *The Period April, 1957–August, 1958*

Since the investigation of methods of treatment during this period established that the use of certain techniques reduced staphylococcal colonization of the umbilicus, a comparison of the incidence of infant sepsis in all of the five series was made. The results are shown in Figure 2. Statistical analysis showed that the differences observed are not significant. During this period infants in groups with high incidence of umbilical stump colonization were nursed in the same wards as infants with low incidence of colonization. It was therefore decided to compare the incidence of sepsis in the upper and lower wards of the Unit during a period when the umbilical stumps in one ward were treated by a technique known to reduce the incidence of colonization while in the other ward they were treated by a technique associated with a high incidence of colonization.

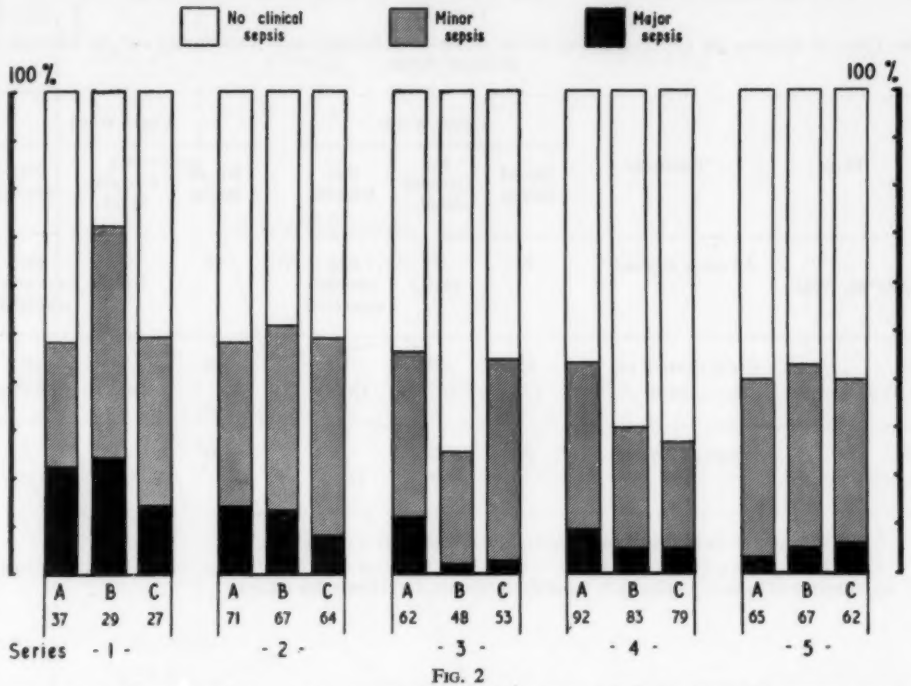

FIG. 2

The effects of vario. techniques of treatment of the umbilical stump on the incidence of neonatal sepsis, observed wit.:in the first three weeks of life. Major and minor sepsis are defined in the text. See Table I for the details of treatment.

(2) *Comparison of Incidence of Sepsis in Two Wards Differently Treated August, 1958–September, 1959*

This investigation comprised three phases consecutive in time (see Fig. 3). In the first all umbilical stumps in both wards were treated by the standard non-occlusive technique with daily spirit swabbing. In the second stumps in the upper ward were again treated as in Phase 1, but in the lower ward of the Unit all the cord stumps were enclosed with cord powder (N.F.) in a keyhole dressing, secured with a binder and left covered for seven days. In the third all stumps in both wards were occluded by the same cord powder, keyhole dressing technique. In all three phases rubber bands were used to ligate the cord.

In Table II the incidence of staphylococcal colonization in these phases is recorded. It will be seen that the use of the occlusive technique again produced a highly significant reduction in the incidence of staphylococcal colonization.

The incidence of neonatal and maternal sepsis in the three phases is shown in Figure 3 and analyzed in Tables II and III. In all phases there is an evident correlation of neonatal sepsis and umbilical colonization. In Phase I neonatal sepsis, although of minor degree, was of epidemic proportions and was followed in Phase II by an outbreak of major sepsis in mothers and infants. But in Phase II there was a significant reduction, not only in the incidence of staphylococcal colonization of the umbilical stump, but also in the incidence of neonatal

TABLE II

The Effect of Covering the Umbilical Stump on the Incidence of Staphylococcal Colonization and the Incidence of Neonatal Sepsis

Phase	Treatment	Lower Ward			Upper Ward		
		No. of Babies	No. Carrying Staph.	No. Infected	No. of Babies	No. Carrying Staph.	No. Infected
I .. .. .. (October, 1958)	All cords exposed	29	25 (86%)	Not recorded separately	30	26 (86%)	Not recorded separately
II .. .. (1.11.58–13.1.59)	Cords covered on lower ward	65	33* (50·7%)	13† (20%)	70	56 (80%)	37† (52·8%)
III .. .. (14.1.59–28.2.59)	All cords covered	49	26* (53%)	3 (6%)	43	23* (53%)	8 (18%)

* The reduction in incidence of colonization is highly significant ($P<0·001$).

† The reduction in incidence of infection in Phase II on the lower ward is highly significant. (The standard error of the difference of these two values is 8·3 and the difference is 3·9 times this value.)

TABLE III

Statistical Analysis of the Incidence of Neonatal Sepsis During the Three Phases of Treatment from August, 1958–February, 1959

Phase	No. of Babies	Neonatal Sepsis		Difference of Incidence	Standard Error of the Difference	Significance* (Diff. ÷ S.E.)
		No. of Babies	Incidence			
I 1.8.58–31.10.58	208	94	45%	I–II 15%	6·0	2·5
II 1.11.58–13.1.59	165	50	30%	II–III 21·7%	4·3	5·0
III 14.1.59–31.3.59	168	14	8·3%	I–III 36·7%	4·6	7·9

* A difference which is greater than twice the standard error is accepted as significant.

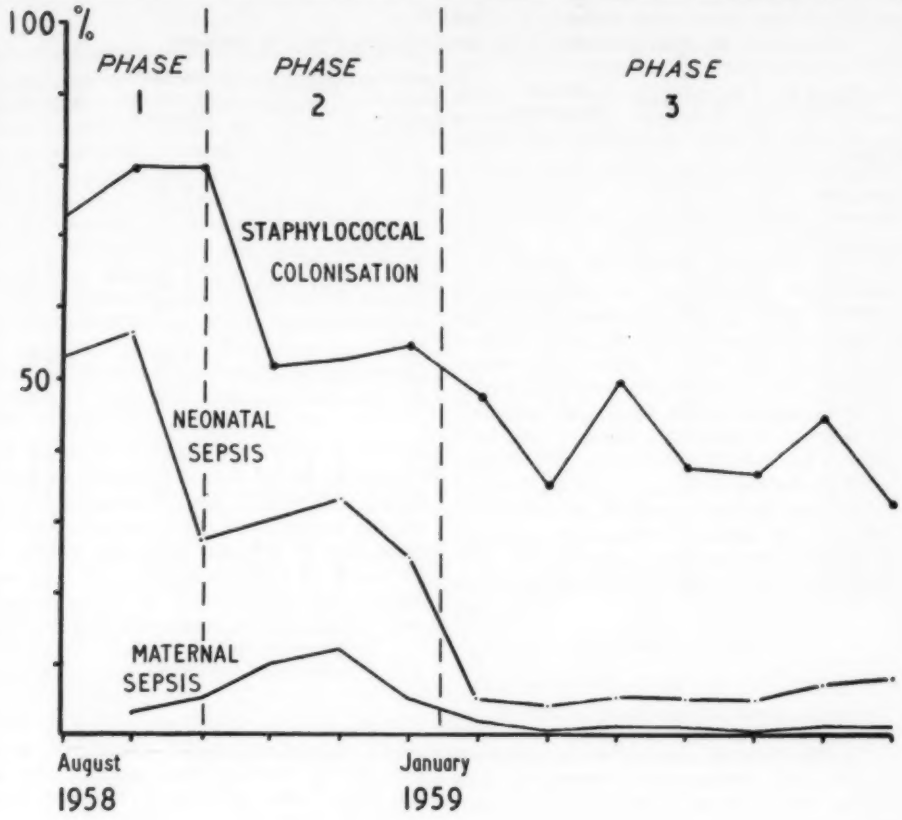

FIG. 3

The correlation between staphylococcal colonization of the umbilical stump and the incidence of neonatal and maternal sepsis. The incidence of staphylococcal colonization and neonatal and maternal sepsis is expressed as a percentage of the total number of babies or mothers in the ward each month. Neonatal sepsis includes major and minor lesions. Maternal sepsis includes only staphylococcal infections, the majority of which were breast abscesses.

sepsis on the lower ward compared with that on the upper ward (Table II). Phase III, when the occlusive technique was used in both wards, was characterized by a further significant fall in umbilical colonization, maternal and neonatal sepsis.

D. OTHER OBSERVATIONS

(1) *Effect of Umbilical Stump Treatment on the Time of Its Separation*

The time of separation was noted in a total of 820 infants, in all groups of the five series.

TABLE IV

The Effect of Umbilical Stump Treatment on the Time of its Separation

Treatment*	No. of Cases	Day of Separation†	Standard Deviation in Drugs	Difference of Means	Standard Error of the Difference	Significance‡ (Diff. ÷ S.E.)
1st Series:						
Group A ..	36	8·5	1·5	A – B 1·5	0·69	2·1
Group B ..	25	10·0	2·1	B – C 1·8	0·56	3·2
Group C ..	26	8·2	1·9	A – C 0·3	0·62	0·4
2nd Series:						
Group A ..	67	8·34	2·1	A – B 1·7	0·53	3·2
Group B ..	62	10·0	2·2	B – C 0·6	1·64	0·4
Group C ..	56	9·4	1·8	A – C 1·1	0·93	1·1
3rd Series:						
Group A ..	57	7·8	2·25	A – B 3·9	0·80	4·8
Group B ..	40	11·7	3·16	B – C 3·8	0·77	4·9
Group C ..	52	7·9	1·55	A – C 0·1	0·52	0·2
4th Series:						
Group A ..	88	8·3	1·8	A – B 1·8	0·49	3·6
Group B ..	80	10·1	2·7	B – C 2·3	0·39	5·8
Group C ..	75	7·8	1·6	A – C 0·5	0·38	1·3
5th Series:						
Group A ..	51	6·3	1·57	A – B 0·3	0·52	0·5
Group B ..	57	6·6	1·83	B – C 0·65	0·47	1·3
Group C ..	48	7·25	1·6	A – C 1·0	0·51	1·9
				Group A (1st–4th series) :: Group B (5th series)=1·9	0·40	4·7

* The key to the treatment is given in Table I.
† Cord shed in the 24 hours preceding the time stated.
‡ A difference which is greater than twice the standard error is accepted as significant.

These results are summarized in Table IV. The application of antibiotics and antiseptics significantly delayed the separation of the cord, whereas there was no difference in the time taken for the cord to separate in the control groups and those treated by covering the cord.

(2) *Organisms Other than* Staphylococcus aureus *Isolated from the Umbilical Stump During the Survey*

A variety of organisms, predominantly coliforms, were isolated (Fig. 1). In the vast majority of cultures growth was sparse and in striking contrast to the profuse growth of *Staph. aureus* obtained when this organism was present. No evidence of maternal or neonatal infection due to organisms other than *Staph. aureus* was obtained.

(3) *Antibiotic Sensitivities of Staphylococcus Isolated*

Although there were fluctuations in the incidence of staphylococci of different antibiotic sensitivity patterns throughout the period of observation, the great majority were penicillin-resistant and typical so-called "hospital staphylococci". No significant correlation could be found between the variation in incidence of organisms with different antibiotic sensitivity patterns and the method of treating the umbilical stump or the incidence of maternal and neonatal sepsis.

Conclusion

(1) The neonatal umbilical stump is obviously extremely susceptible to colonization by bacteria and the observations presented here probably reflect the state of affairs which will obtain in the maternity unit of any general hospital which harbours a population of staphylococci. Using a non-occlusive technique it appears that the umbilicus is colonized at birth or in the 24-hour period following delivery and that virtually all infants are affected. This finding and the patterns of antibiotic sensitivity observed suggest that the spread is from staff to umbilical stump and supports the view (Forfar *et al.*, 1953; Jellard, 1957) that the spread of staphylococcal infection in maternity units is from staff to infants and from infants to mothers.

(2) Although the umbilical stump is not the original or, indeed, the only source of staphylococci in a maternity unit, the profuse growths invariably obtained in this investigation indicate that it is an important reservoir of pathogenic organisms. Any scheme designed to reduce or eliminate sepsis in a maternity unit should therefore include measures to reduce the incidence of umbilical stump colonization.

The investigations reported here indicate that certain techniques of management of the umbilical stump are more effective in this respect than others. Of these techniques occlusion with keyhole dressing, cord powder and binder seems the simplest and, since it does not require that antibiotics or antiseptics should be used, perhaps the most desirable.

(3) The effects on sepsis of reducing stump colonization by this occlusive technique have been described. During the period April, 1957 to August, 1958, when infants with low incidence of colonization were nursed in the same ward as those with a high incidence, there was no reduction in sepsis. If it is accepted that the colonized umbilical stump is an important reservoir of staphylococci, the unchanged incidence of sepsis during this period is not unexpected since at least two-thirds of the infant population were heavy carriers. During the period August, 1958 to September, 1959 (Fig. 3) the application of the occlusive technique, first to one and then to both wards, was associated with a significant reduction in both sepsis and colonization. This strongly suggests a cause and effect relationship between colonization and sepsis; nevertheless some caution in interpreting these results is necessary. No major changes in the organization of the wards were made during this period; important preventive measures such as "rooming-in", isolation of mother and infant as a unit if either developed a septic lesion, and prompt or early discharge, whenever possible, of infected mothers and infants had been observed for some considerable time before the period under discussion. Therefore it seems reasonable to assume that reduction or prevention of umbilical colonization and the encouragement of early separation of the stump should be among the measures taken in any assault on sepsis in a maternity unit. The findings presented here indicate that the occlusive technique described is effective in this respect.

Acknowledgments

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THE RELATIONSHIP BETWEEN ANTIBIOTIC THERAPY AND STAPHYLOCOCCAL SENSITIVITIES IN A MATERNITY HOSPITAL

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IN the early months of 1950 it became evident that the staphylococci in the newborn nurseries in St. Mary's Hospitals, Manchester, were becoming increasingly resistant to penicillin and it was decided to withdraw the drug from routine practice in the neonatal department. Since that time penicillin has been given only when the sensitivities of the cultured organism have justified its use.

Streptomycin was selected as the routine antibiotic and the dosage was based on a scheme recommended by Professor W. F. Gaisford, viz., a single dose of 125 mg. in the morning for infants weighing 6 pounds and over and 62·5 mg. for infants weighing less than 6 pounds. The dose was to be repeated after intervals of 12 hours or 24 hours but only after consultation on each occasion. Initially totals up to 750 mg. were given in certain cases but for the last six years a maximum of 400 mg. has been used and the average total has been 250 mg. Other antibiotics have been prescribed when clinically and bacteriologically indicated and recently erythromycin and chloramphenicol have been the drugs of choice when more prolonged treatment has been indicated. Antibiotic therapy was used in a small percentage of cases only, as the simple superficial lesions were treated with local applications of antiseptics or triple dyes.

There are many critics of streptomycin in infancy, and deafness and vestibular damage are cited as serious complications. Recently 84 children who had received 375 mg. streptomycin or more during the newborn period were reviewed by Dr. I. H. Taylor of the Department of Education of the Deaf, University of Manchester. After repeated testing in several doubtful cases only two children were found to have a definite impairment of hearing. One was an infant who had *Escherichia coli* meningitis and was grossly retarded, both mentally and physically. The second child had received 375 mg. streptomycin for a severe respiratory infection. We do not believe there were any cases of vestibular damage in the whole series but we hope to investigate this aspect of the problem in greater detail.

This approach was not paralleled in the obstetric wards where penicillin, either alone or in conjunction with streptomycin, was given for some years in addition to sulphonamides; more recently the tetracyclines have been used in considerable quantities following the work of Smith and Smith (1954).

In view of the great concern which exists currently in respect of the increasing resistance of the staphylococcus we have analyzed the sensitivities of strains of *Staph. pyogenes*

TABLE I

Staphylococci Isolated from Babies 1958/1959

	1958		1959		Total	
	No.	%	No.	%	No.	%
No. isolated	307		275		582	
Sensitive to all antibiotics	32	10·4	29	10·6	61	10·5
Resistant to:						
Penicillin	260	85	243	88	503	86
Streptomycin	130	42·5	98	35·5	228	37
Chloramphenicol	10	3·25	6	2·2	16	2·75
Tetracycline	104	34	81	29·5	185	32
Erythromycin	0	0	0	0	0	0
Novobiocin	9	2·9	0	0	9	1·5
Penicillin only	129	42·4	147	54	276	47·5
Penicillin and streptomycin	36	11·8	14	5·1	50	8·6
Penicillin, streptomycin and tetracycline	71	23	76	27·5	147	25

TABLE II

Staphylococci Isolated from Mothers 1958/1959

	1958		1959		Total	
	No.	%	No.	%	No.	%
No. isolated	256		263		519	
Sensitive to all antibiotics	59	23	67	25·5	126	24·5
Resistant to:						
Penicillin	169	66	185	70·5	354	68
Streptomycin	116	45	113	43	229	44
Chloramphenicol	12	4·6	5	1·9	17	3·3
Tetracycline	116	45	134	51	250	48
Erythromycin	0	0	0	0	0	0
Novobiocin	10	3·9	9	3·4	19	3·7
Penicillin only	35	13·6	52	19·8	87	16·8
Penicillin and streptomycin	24	9·3	7	2·6	31	6
Penicillin, streptomycin and tetracycline	60	23·2	101	38·5	161	31

(coagulase positive) isolated from newborn babies and their mothers in the years 1958–1959.

The sensitivity tests were carried out by the dried disc technique (Fairbrother and Martyn, 1951) with the amounts of antibiotic per disc as follows:

Penicillin	1·5 units
Streptomycin	30 μg.
Chloramphenicol	30 μg.
Tetracycline	30 μg.
Erythromycin	10 μg.
Novobiocin	10 μg.

The sensitivities of staphylococci isolated from babies is shown in Table I and those of the staphylococci isolated from mothers in the same wards in Table II. The more significant alterations in certain resistant organisms are best shown diagrammatically (Fig. 1).

The staphylococci were isolated mainly from sticky eyes, skin pustules and the umbilicus in the babies and from the uterus and urine in the mothers. A small number came from other lesions, such as abscesses, in both groups.

During the two years under review the resistance to penicillin has not altered appreci-

ably. The difference in resistance between the strains from maternal sources and those from babies emphasizes the fact that, whereas virtually all the staphylococci colonizing or infecting babies are "hospital staphylococci", many of the staphylococci from mothers are brought into the hospital. The difference between "hospital" and "outside" staphylococci has been clearly shown by several authors (Clarke, Dalgleish and Gillespie, 1952; Parker, 1958; Florey and Ungehauer, 1958; Goodier and Parry, 1959).

There has been no significant change in the number of organisms resistant to streptomycin although the figures presented suggest a reduction in resistant strains, especially in the babies. The overall figure for the two years of 41 per cent resistant to streptomycin is considerably higher than that appearing in other reports and may be accounted for in part by the different strength of antibiotic discs used. Giles and Shuttleworth (1958) showed that although over six years the number of resistant strains was 19 per cent, there was in fact a steady rise during the 6 years, reaching 33 per cent in 1956.

The striking feature is the high tetracycline-

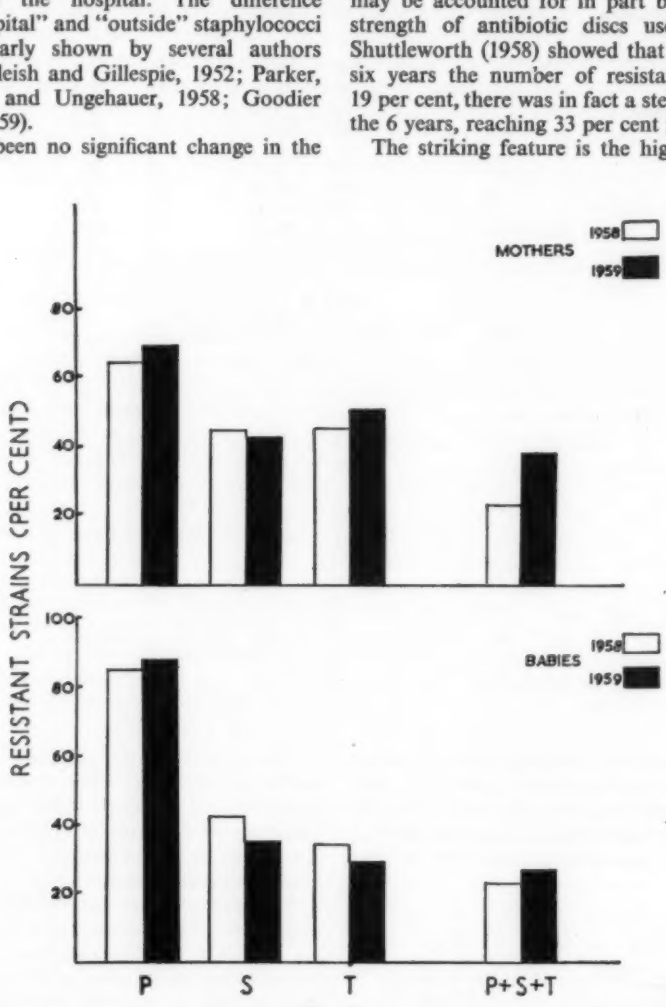

FIG. 1

Resistance to various antibiotics of staphylococci isolated from mothers and babies in 1958 and 1959. P=penicillin. S=streptomycin. T=tetracyclines.

resistant rate and the marked increase in this resistance in the organisms obtained from the mothers during the two years. This almost certainly is due to the greatly increased use of the tetracyclines in 1959; approximately 1 kg., being prescribed in 1958, this amount rose to 3·5 kg. in 1959.

The proportion of strains, from babies resistant to all three antibiotics (penicillin, streptomycin and tetracycline), shows a small increase in 1959 (27 per cent) over 1958 (23 per cent), but, whereas in 1958 70 per cent of the staphylococci resistant to tetracycline were also resistant to penicillin and streptomycin, in 1959 this proportion rose to 95 per cent. This trend towards multiple resistance strains was more marked in the mothers, 23 per cent being resistant to all three antibiotics in 1958 rising to 38 per cent in 1959 (an increase of 60 per cent) with the proportion of tetracycline resistant strains also resistant to penicillin and streptomycin rising from 52 per cent to 72 per cent. The higher proportion of multiple resistant strains in babies presumably is because nearly all their lesions are caused by hospital staphylococci in which a high degree of multiple resistance is being produced; this was noted by Giles and Shuttleworth (1958) during their 6 years' survey.

The increase in staphylococci resistant to three or more antibiotics has been restricted to the combination—penicillin, streptomycin and tetracycline. The number of strains resistant to other combinations is of no significance and a decrease was seen in 1959 (1·5 per cent) as compared with 1958 (3 per cent). This relatively fortunate state of affairs is due in part to the policy of keeping erythromycin and novobiocin in reserve and not allowing their general use.

We have noted that the staphylococci from superficial lesions (eyes, umbilicus) are on the whole more resistant to antibiotics than staphylococci from deeper lesions (pustules, abscesses). This is in contrast to the findings of Barber and her colleagues (1960) who found the more resistant staphylococci associated with severe infections. This difference might be explained by the fact that pustules and abscesses in babies are "primary" lesions depending partly upon the invasiveness of the particular staphylococcus whereas in adults the severe infections normally occur in patients who have undergone major surgical treatment or who are already suffering from another disease. The preponderance of more resistant organisms in surface infections in babies is a reflection of the high incidence of resistant staphylococci in the hospital environment.

A representative selection of the staphylococci were "phage"-typed by Dr. M. T. Parker. The most common types isolated from deeper lesions belong to Group 1 (29, 29/52, 52A) whereas the

TABLE III

Variation in Resistance of Staphylococci in Relationship to Site of Infection

	Surface		Deep	
	No.	%	No.	%
No. isolated	350		232	
Sensitive to all antibiotics	38	10·8	23	9·8
Resistant to:				
Penicillin	299	65	204	85
Streptomycin	—	—	—	—
Chloramphenicol	10	2·7	6	2·5
Tetracycline	128	36	57	24
Erythromycin	0	0	0	0
Novobiocin	9	2·5	0	0
Penicillin only	141	40	135	58
Penicillin and streptomycin	34	9·7	16	6·9
Penicillin, streptomycin and tetracycline	105	30	42	18

more resistant strains found in the conjunctiva and on the umbilicus belong to Group 3 (mainly 7/47/53/54).

This broad association of the phage group with the invasiveness of the infection has been demonstrated previously (Parker, 1958).

From this personal experience we feel that a good case can be made out for the use of streptomycin in the treatment of infections in infancy, certainly until cultures and sensitivities become available. Emphasis should be placed on "stoss-therapeutic" approach and the restriction of the total quantity of streptomycin used.

We suggest also that tetracyclines could be withdrawn from the drug cupboard of the newborn nursery as:

(*i*) Tetracyclines have little advantage over streptomycin as far as laboratory sensitivities tests are concerned and the difference is more than balanced by the fact that streptomycin is bactericidal in effect;

(*ii*) There is the possibility of entero-colitis developing in cases treated with tetracyclines;

(*iii*) A reduction in the use of tetracyclines in babies and their mothers should allow of an increase of tetracycline sensitive organisms in the hospital and the incidence of staphylococci resistant to several antibiotics including tetracyclines might well be reduced;

(*iv*) It can be seen from our figures that after many years of this regime we have several antibiotics left that can be used with confidence should streptomycin therapy be either ineffective or contra-indicated, or when the total amount needed exceeds 400 mg.

Summary

(1) A description is given of the antibiotic policy employed in the neonatal department of the hospital since 1950.

(2) Details are given of the sensitivities of the staphylococci obtained from mothers and babies in the years 1958 and 1959.

(3) In the light of these findings suggestions are made concerning the future use of antibiotics in the maternity hospital.

We wish to thank Professor W. F. Gaisford for his interest and original suggestions for streptomycin therapy, Dr. M. T. Parker for carrying out the typing of the staphylococci and Dr. I. H. Taylor for his very willing co-operation.

Addendum

When the rapid increase in multiple resistant strains of staphylococci in 1958 and 1959 became known, a system of stricter control of antibiotic therapy was instituted in February, 1960. This resulted in a marked reduction in the amount of penicillin, streptomycin and tetracycline used and also a reduction in resistant strains especially to combinations of antibiotics. For example only 1·5 kg. of the tetracyclines was used in 1960 instead of 2·5 kg. in 1959 and tetracycline resistant strains fell from 29 per cent to 17 per cent in babies and from 51 per cent to 22 per cent in mothers. Strains resistant to penicillin, streptomycin and tetracycline fell from 25 per cent to 11 per cent in the babies and from 30 per cent to 14 per cent in mothers.

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THE DETECTION OF AN OUTBREAK OF STAPHYLOCOCCAL INFECTION OF PERINEAL TEARS BY ROUTINE PHAGE TYPING

BY

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THE object of this paper is to present some evidence as to the value of routine phage typing in the study and control of staphylococcal infection in hospitals and to report the successful detection and tracing of an outbreak of perineal wound infection in a maternity ward.

It was thought that it would be of interest to phage type every *Staphylococcus aureus* isolated in the clinical laboratory for a period of time in order to find out the number of different types causing infections, whether any particular types predominated, the frequency with which "dangerous" strains such as type 80 occurred and to see if routine phage typing helped in the early detection of epidemics due to single strains.

In one instance routine phage typing was conspicuously successful in enabling a small outbreak to be detected, traced to its source in a carrier and effectively dealt with.

METHODS

(1) The strains of staphylococci were isolated on blood agar and identified by colonial appearance and slide coagulase test. They were stored on agar slopes in bijou bottles and phage typed by the method of Anderson and Williams (1956) as soon as possible, the results being recorded in a book ward by ward.

(2) The methods used to investigate the carrier were those described by Hare and Ridley (1958).

RESULTS

General

During the five-month period of this survey there were 227 cases of staphylococcal infection severe enough for material to be sent to the laboratory for examination. In all but 56 cases the staphylococcus could be typed with the routine set of phages.

Staphylococci belonging to Groups I and III caused far more infections than those of Group II. Some of the wards showed a tendency for infections arising therein to be caused by identical or closely related phage types which differed from the strains prevalent in other wards. This suggests that these infections were a result of cross-infection within the ward rather than auto-infections or theatre infections.

Staphylococcal Epidemics

There were several occasions when the results of phage typing suggested that two or more cases of infection might be related.

(1) Two patients in the same ward developed infections due to type 52/52A/80 at the same time, when there had been no previous infections due to this strain.

(2) Three patients and a nurse all became infected about the same time with type 80 in a ward previously free of this strain.

(3) A number of type 83 infections were scattered throughout several wards at the same time.

Enquiry showed in these instances that, although a plausible connexion between the cases in the first and second outbreaks could be made out, there appeared to be no connexion between the cases in the third outbreak nor any evidence to suggest that swabbing of nurses or operating teams might prove useful.

In a fourth series of infections phage typing

provided valuable data and this outbreak will be described in detail.

Epidemic of Perineal Wound Infections in the Maternity Ward

Between 4th and 27th November there were seven cases of staphylococcal infections in the maternity unit due to the following six different phage types: 29/52/52A/80/7, 80, 80/47+, 52/80, 52/52A/80/73 and an untypable strain but between 28th November and 3rd December there occurred three new cases all due to type 3c/55/71. They were all infected perineal tears and enquiry elicited the fact that the only person who had attended all three patients was the house surgeon who had sutured all three perineums.

He was found to carry the same strain of staphylococcus in his nose and on his hands. A survey showed that amongst the other attendants at the deliveries there was a student who carried the same type in his nose and a sister with type 3c/55 in her nose, but neither of these persons had attended all the deliveries and they had both been absent from one. It was, therefore, assumed that the house surgeon was the cause of the outbreak.

On 15th December a complete survey of his skin and clothing was carried out, the results of which are given in the Table (Table I). Single colonies from each of the sites were phage typed and it will be seen that he was not only heavily contaminated but that the epidemic type was present on the majority of sites. Another type (6/7/42E/54/73/75) was found on the hair, chest, back and perineum.

TABLE I

	15th December		21st December		4th January		11th January
	Initial Body Survey Results		Survey After 5 days' Treatment with Naseptin and Cidal Soap		Survey 14 Days After Discontinuing Naseptin but Continuing with Cidal Soap		Survey After 5 More Days' Treatment with Naseptin
Left nostril ..	500+	3C/55/71	0		500+	3C/55/71	0
Right nostril ..	500+	3C/55/71	0		500+	3C/55/71	0
Throat	0		0		0		0
Hair	100+	6/7/42E/54/73/75	0		0		0
Chest	150	6/7/42E/54/73/75	1	6/7/42E/54/75+	40	3B/6/7/42E/54/75+	0
Back	150	6/7/42E/54/73/75	1	6/7/42E/54/75+	37	3B/6/7/42E/54/75+	0
Abdomen	70	3C/55/71	0		0		0
Perineum	40	7/42E/54/75+	0		0		0
Right thumb ..	17	3C/55/71	0		1		0
Right 1st finger ..	16	3C/55/71	0		0		0
Right 2nd finger ..	43		0		0		0
Right 3rd finger ..	120	3C/55/71	0		0		0
Right 4th finger ..	18		1	3C/55/71	400+	3C/55/71	0
Left thumb ..	8	3C/55/71	0		10		0
Left 1st finger ..	3	3C/55/71	0		8		0
Left 2nd finger ..	6	3C/55/71	1	6/7/42E/54/75+	2		0
Left 3rd finger ..	7	3C/55/71	1	6/7/42E/54/75+	72		0
Left 4th finger ..	120	3C/55/71	0		65	3C/55/71	0
Shirt	5	3C/55/71	0		14	3C/55/71	0
Coat back ..	10	3C/55/71			1		
Coat front	4	3C/55/71			1		0
Pants back ..	2	3C/55/71	2	6/7/42E/54/75+	0		
Pants front ..	6	3C/55/71	1	3C/55/71	0		0
Trousers	17	3C/55/71	4	3C/55/71	0		0
Dispersal per square feet per mm. ..	22·4		<1·0		not done		<1·0

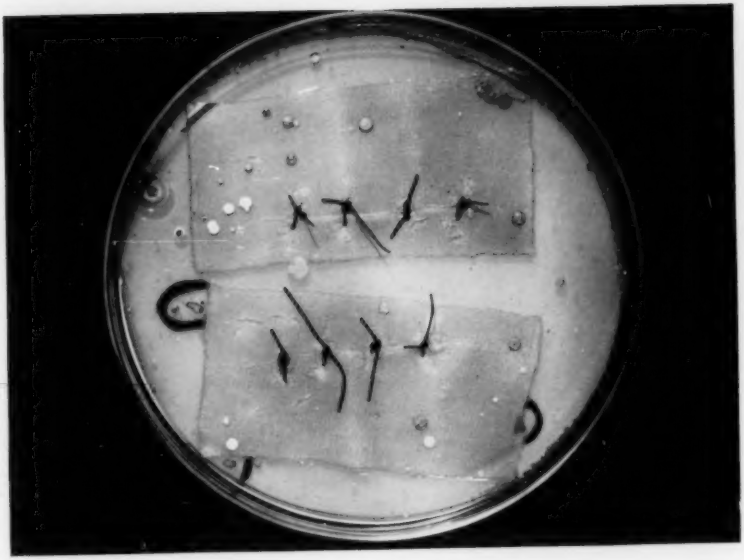

FIG. 1

"Mock operation"—colonies of the infecting strain of *Staph. aureus* ringed in black.

On the same day his ability to disperse staphylococci while exercising was investigated and it was found that while exercising he was able to disperse staphylococci to the extent of 22·4 staphylococcal bearing particles settling per square foot per minute. Comparison with the results of Hare and Ridley shows that he was not only an unusually heavily contaminated carrier but a prolific disperser.

Because of these results, it was decided to determine whether he was able to contaminate culture plates when carrying out the same manœuvres involved in suturing a perineum. For this purpose he scrubbed up, donned gloves, sterile gown, mask and cap and, using sterile instruments, incised and then stitched together again pieces of lint which had been embedded in nutrient agar contained in large petri dishes measuring 22·0 cm. in diameter. The whole "operation" was carried out in the labour ward. Each plate took 10 minutes and three such plates were dealt with in succession. Immediately before he started the 3rd plate the glove fingers of the thumb and forefinger were deliberately punctured (Fig. 1).

After incubation there were three colonies of *Staph. aureus* of the epidemic type on the first plate but none on the other two. They were some distance from the suture lines but it is evident that, in some undetermined way, he had been able to contaminate the field of operation. This added weight to the evidence that he was probably responsible for the outbreak.

He had no gross superficial lesions himself but the skin of the face and forehead showed a mild furunculosis from which the epidemic strain of staphylococcus was recovered.

He was taken off duty and treated with intranasal "Naseptin" four times daily for five days and used hexachlorophene soap for bathing and washing. A second survey on 21st December showed a marked reduction in number of staphylococci on his person only a few of which were of the epidemic type. He then discontinued the intranasal "Naseptin" for 14 days when a third survey was carried out. Considerable numbers of the epidemic type had reappeared in the nose, on the fingers and shirt. He was given another five-day course of "Naseptin" and a further survey showed no staphylococci on his person nor did he disperse any in the cubicle.

Although the house surgeon had resumed his duties immediately after the first course of treatment and a number of cases of sepsis occurred in the maternity unit none was due to the types of staphylococci carried by him.

Discussion

The work draws attention to the possible value of prompt phage typing of all strains of staphylococci isolated from infections within a hospital since it permits the early detection of small epidemics and helps in discovering the probable source. Nevertheless the considerable labour involved is probably out of proportion to the useful results obtained.

In the outbreak described there was much evidence to suggest that the house surgeon was, in fact, the source of the organisms. Not only was he a heavy nasal carrier but his skin and clothing were much more heavily contaminated than is usual with nasal carriers (see Hare and Ridley, 1958) and he was a more than usually prolific disperser. He was also able to contaminate a culture plate on which he was performing the same manipulations involved in suturing a perineal tear. In this he resembles in some respects the theatre nurse described by Penikett *et al.* (1958) and Sompolinsky *et al.* (1957) who contaminated instruments and sutures causing outbreaks of infection and the members of the operating team described by Shooter *et al.* (1957).

Exactly how these organisms reached the culture plate was not determined. The gloves were not punctured and he did not speak during the operation. It might be conjectured that they fell on skin scales from his face or forehead which were known to be contaminated with the epidemic type. It is thus evident that an unusually heavy carrier can in some way cause contamination of an open wound.

It is also of interest that although he had caused infection in three successive perineums he had sutured, following treatment with "Naseptin" and hexachlorophene soap, he was able to return to his duties without causing any further infections.

Summary

An account is given of a small outbreak of staphylococcal wound infection which was detected and traced to its source in a carrier by routine phage typing of all strains of *Staph. aureus* isolated in the clinical laboratory.

I wish to thank the staff of the Louis Jenner Laboratory, St. Thomas's Hospital, for providing cultures of all the strains of staphylococci isolated, Miss K. Gregory for her technical assistance and Professor R. Hare for help in the preparation of this paper.

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THE IMPORTANCE OF PLACENTATION EVIDENCED BY DENERVATION OF THE INTERNAL ILIAC VESSELS

BY

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THE purpose of this paper is to report further experience gained from denervating the internal iliac vessels, to contrast these results with those following a saddle-shaped embolus occurring at the 31st week of pregnancy, and to stress the fundamental importance of actual placental formation. It follows from these observations that maternal defects may precede the pregnancy and be the cause of eclampsia and "toxaemia", and that "toxaemia" occurring in association with an inadequately formed placenta may differ in many respects from that occurring after the placenta is well formed. Seeing that the sphygmomanometer is used more frequently in obstetrics than in any other branch of medicine, and that denervation of the internal iliac vessels may prevent the onset of hypertension, a few observations are included concerning the opportunity afforded to obstetricians to contribute to the wider problem of raised blood pressure.

The terms "toxaemia" and "pre-eclampsia", which confuse rather than illumine, will be avoided, and cases will be described in terms of hypertension (H), proteinuria (P), oedema (O), oliguria (U), all of which can be measured, and of symptoms, such as headache, visual disturbances, epigastric pain and vomiting (S).

DENERVATION OF THE INTERNAL ILIAC VESSELS

In 1934 Theobald reported that afferent nerve stimuli varying in intensity from attempts at lumbar puncture to shaving the skin in preparation for it, sufficed to inhibit water diuresis in the dog and that the urine subsequently passed in small amounts usually contained protein. Indeed, ostentatious preparations for lumbar puncture inhibited water diuresis in conditioned dogs. He argued that if the prick of a needle in the lumbar region sufficed to cause these effects on the kidneys, afferent impulses from the uterus might have similar effects. In April, 1947 he treated a patient with severe pregnancy HP+ by injecting local anaesthetic into the renal plexus on either side, and repeated this procedure on a number of patients and often on several occasions. Later he tried paravertebral block with a view to overcoming spasm of arteries from which those supplying the uterus arose. The only encouragement was apparent slight temporary improvement.

In January, 1950 he denervated the internal iliac vessels of a patient who had had HP+ in two previous pregnancies, with the idea of increasing the blood supply to the placenta (Theobald, 1953). He realized that this procedure, if effective, might operate: (1) by increasing the blood supply to the uterus; (2) by cutting off afferent and efferent impulses travelling from and to the uterus along sympathetic pathways. He included evidence that such nervous impulses could affect the blood pressure (see also Sophian, 1953).

This operation has now been performed 14 times. All trace has been lost of the first patient, who had Raynaud's disease for which cervical sympathectomy had already been done. She was deteriorating when last seen and it is assumed that she did not become pregnant. Seven patients have had one or more successful pregnancies

subsequent to the operation, five failed to conceive, a further one is now pregnant and one who was done recently is likely to conceive.

The operation, which will subsequently be referred to as "denervation", consists essentially in stripping the nerve fibres, not merely the loose areolar tissue, from the internal iliac vessels and the lower portion of the common iliac arteries. The tissue concerned is closely applied to the vessel wall and its removal sometimes causes oozing from it. The surprising fact was the small size of the internal iliac arteries in these patients, the diameters of which increased subsequent to denervation. The risk of haemorrhage was lessened by passing one ligature round the upper part of the internal iliac artery, and two round the vein, the one at the upper and the other at the lower part of it. Traction on these ligatures controls bleeding which may be troublesome.

In two patients the infundibulo-pelvic ligaments were divided between ligatures and then approximated. Pre-sacral neurectomy was not always done. After the fourth operation the internal iliac vessels and the exposed portions of the ureters were painted with either 5 or 6 per cent phenol, and on some occasions the uterine arteries themselves were exposed and painted with it.

This operation is not advocated if the blood pressure exceeds 140/90 mm. Hg in the non-pregnant state, for in such a patient a wider sympathectomy is indicated (Kellogg, 1945; Newell and Smithwick, 1947; Peet and Isberg, 1949). Neither is it perhaps advisable until the woman has lost two babies in association with HP+, as very occasionally a woman may have HP+ and lose her first baby before the 34th week of pregnancy and yet have subsequent normal pregnancies (Theobald, 1953). The trouble is that after two unsuccessful pregnancies the woman, her husband and notably her doctor, may oppose a third pregnancy.

The small size of the aorta, of the iliac arteries and also of the renal arteries, is illustrated in the arteriogram shown in Figure 1 (Case 10), which may be compared with that from a patient with a renal cyst shown in Figure 2.

An arteriogram from Case 13 (Fig. 3) shows not only a small aorta and small iliac arteries, but an abnormal leash of vessels which enters the upper pole of the right kidney and provides its sole blood supply. These arteriograms (Figs. 1 and 3) suggest that the observed hypoplasia of the iliac vessels may affect the whole arterial tree and in consequence the blood supply to organs and glands.

Case Reports

The five patients who failed to conceive after denervation will be disposed of first, and this arrangement makes it impossible to number the cases in chronological sequence. Nothing more need be said about the patient with Raynaud's disease or the patient who has been done recently. The other patients were subfertile and all are well with present blood pressure values varying from 140–150/80–100, with the exception of Case 4, who is suffering from symptoms related to hypertension. Her blood pressure was 160/90 when she booked in 1952, at the age of 22, when 26-weeks pregnant. It is evident that she was not a suitable person for denervation, which was done in 1953, although, curiously enough, denervation combined with pre-sacral neurectomy completely relieved her severe headaches for three years. They have since recurred

The patients who got pregnant subsequent to denervation will now be reported in further detail. The amount of protein in the urine will be recorded as P, followed by a number denoting the number of parts (Esbach), the amount of urine secreted in 24 hours as U, followed by the number of ounces; A.R.M. will denote artificial rupture of the membranes, and I.V.P., intravenous pyelogram.

Case 6

Gravida-1, *cet.* 26, L.M.P., 4th October, 1946 Booked, 11th February, B.P. 140/90. At 28 weeks, B.P. 200/130, P., 6 parts, headache, vomiting, epigastric pain; right disc showed exudate and haemorrhage. She was delivered of S.B. male foetus, 2 pounds 8 ounces (1·1 kg.), on 24th May.

Second pregnancy. She was 7 weeks in the antenatal ward. B.P. reached 170/120, P., 1 part, poor daily secretion of urine varying between 20 and 60 ounces (570 and 1,700 ml.). At 30 weeks, delivery of S.B. male macerated foetus, 3 pounds 14 ounces (1·8 kg.), on 9th October, 1948.

FIG. 1

Arteriogram from Case 10 before denervation of the internal iliac vessels. The small size both of the abdominal aorta and its branches, and of the renal vessels may be compared with those illustrated in Figure 2.

FIG. 2

Arteriogram of woman with a cyst in the lower pole of the right kidney.

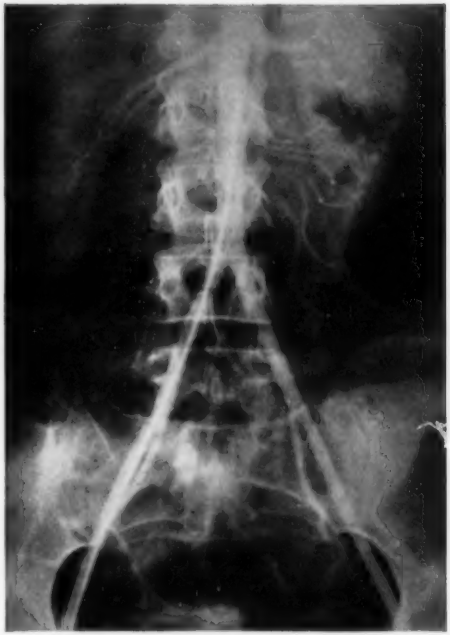

FIG. 3

Arteriogram from Case 13 before denervation. It shows not only the small size of the abdominal aorta but a small leash of vessels entering the upper pole of the right kidney which forms its only blood supply. The above aortograms were made by Dr. R. J. Carr.

FIG. 4

Arteriogram taken during the puerperium. The lower end of the abdominal aorta is completely blocked by the embolus, as neither common iliac artery can be envisaged.

FIG. 5

Photograph of embolus successfully removed by Professor Fitzgerald some 10 weeks after its formation. The clots plugging the internal iliac arteries are clearly seen. I am greatly indebted to Dr. R. G. W. Ollerenshaw, Department of Medical Illustration, Manchester, for rephotographing Figures 3, 4 and 5. Figures 1, 2, 4 and 5 are reproduced from *The Pregnancy Toxaemias* (pages 232, 233, 321, 322) by G. W. Theobald, by kind permission of the Publishers, Messrs. H. Kimpton.

24th January, 1950, denervation of noticeably small internal iliac vessels, appendicectomy, and partial resection of right ovary.

Third pregnancy. L.M.P., 5th September, 1950. B.P. 120–138/74–84 until 37 weeks. Highest B.P., 150/90, settled to 130/90 in ward. 11th June, induction of labour, female infant 6 pounds 7 ounces (2·9 kg.). B.P. rose during puerperium to 160/105 and then returned to normal.

Fourth pregnancy. 20th February, 1957, spontaneous delivery of S.B. female foetus, 2 pounds 4 ounces (1 kg.), at 35 weeks, after 15 weeks in the antenatal ward. The highest B.P., 190/110, was noted on the 6th day of the puerperium. It is presumed that sympathetic control of the internal iliac vessels had become re-established.

Case 7

Gravida-3, *aet.* 35, married 10 years, first seen by me in May, 1949, at infertility clinic. First pregnancy, 1941, "injected away" because of kidney trouble; second pregnancy, 1943, premature S.B. foetus at seventh month, "kidney trouble and blood pressure".

Third pregnancy (first in Bradford): L.M.P., 12th November, 1949; 2nd February, at 12 weeks, B.P., 150/90; from 8th March to 17th June, B.P. 100–120/60–80. 1st July, B.P. 168/100, P., 2½ parts, U., 66–138 ounces (1,875–3,920 ml.). Highest B.P., 200/120. At 37 weeks, S.B. macerated female foetus, 4 pounds 10 ounces (2·1 kg.). Very small placenta. B.P. rose on 5th day of puerperium to 200/100 mm. Hg.

24th October, 1950, denervation, pre-sacral neurectomy, division of both infundibulo-pelvic ligaments, and partial resection of left ovary.

Fourth pregnancy. L.M.P., 24th March, 1951. Highest recorded B.P. during pregnancy, 136/90, usual variation 110–120/70–80. Labour induced at 38 weeks. 17th December, male infant, 7 pounds 8 ounces (3·4 kg.).

Case 8

Gravida-1, *aet.* 34, infertility patient, congenital absence of left kidney.

First pregnancy. L.M.P., 7th June, 1949. At 12–14 weeks, B.P. 120/80. At 22 weeks, B.P. 170/110, P., 4·5 parts, 0++++, U., 205 ounces (5,825 ml.); papilloedema, almost blind. 7th January, at 30+ weeks, macerated male foetus, 3 pounds 8 ounces (1·6 kg.), following induction of premature labour.

24th January, 1950. "Both eyes show severe hypertensive and albuminuric retinopathy with papilloedema. Retinal changes indicate severe damage to vascular system and the kidneys, and the prognosis as judged from the ophthalmic point of view is not good." The electrocardiogram showed pronounced left axis deviation of hypertension. During the next few months B.P., 110–140/70–90.

2nd February, 1951, denervation, pre-sacral neurectomy, right infundibulo-pelvic ligament divided, denervated vessels and exposed portion of right ureter painted with 5 per cent phenol.

Second pregnancy. L.M.P., 30th August, 1951. Patient nervous, not co-operative, always feared the worst. Only one low B.P. reading (126/76) during pregnancy. B.P. varied from 140–170/90–106, P., 0·5 part, only towards end of pregnancy.

29th April, 1952 (35 weeks), Caesarean section, female infant, 5 pounds 2 ounces (2·3 kg.).

January, 1960, patient and daughter are very well; maternal B.P. 140/80.

Case 9

Gravida-1, *aet.* 22, emergency admission 23rd November, 1949, at 22 weeks. B.P., 170/126, P., 2 parts, U., 116 ounces (3,296 ml.), history of repeated headaches, "faints", and feeling ill for 4 weeks.

28th November, spontaneous delivery of macerated male foetus, 17 ounces (0·5 kg.), retroplacental clot+.

18th July, 1951, denervation, denervated vessels and exposed portions of ureters painted with 5 per cent phenol. Pre-sacral neurectomy not done.

3rd May, 1954, spontaneous delivery of female infant, 6 pounds 8 ounces (3 kg.), after a normal pregnancy.

8th January, 1960, 25-weeks pregnant, very well, B.P. 135/80.

Case 10

Gravida-1, *aet.* 34, infertility patient.

18th August, 1952, 12-weeks pregnant, B.P., 150/90. B.P. dropped to 120/80, and rose again to 190/110 at 29 weeks. O+, U., 97 ounces (2,756 ml.).

8th January, 1953, death of foetus.

17th January, male macerated foetus, 2 pounds 8 ounces (1·1 kg.), following induction of premature labour.

14th April, 1953, denervation with use of 5 per cent phenol. Pre-sacral neurectomy not done.

Second pregnancy. April, 1954, male infant 8 pounds (3·6 kg.). B.P. normal throughout pregnancy except for one rise at 32 weeks. Maternal age, 37.

Case 11

Gravida-1, *aet.* 17, late booked, admitted 6th December, 1955, at 30 weeks, twin pregnancy. B.P. 125–170/75–120, P., 6 parts, O+, U., 14 ounces (398 ml.), vomiting, blood urea 20 mg. per cent, height 5 feet 2 inches, slight build.

4th January, 1956, A.R.M.

5th January, female infants, 2 pounds 2 ounces (1 kg.) died on 5th day, and 1 pound 15 ounces (0·9 kg.) died on 6th day. Placenta small. I.V.P. showed slight hydronephrotic changes and residual dilatation of right ureter.

Second pregnancy. Not booked, notwithstanding HP+ in first pregnancy.

9th January, 1957, emergency admission, 35 weeks, B.P., 150/100, P., 2 parts, U., 13 ounces (370 ml.).

10th January, death of foetus.

12th January, macerated female foetus. Placenta small and badly infarcted.

2nd March, 1957, B.P. 130/60.

15th July, 1957, denervation, pre-sacral neurectomy, denervated vessels and exposed portions of ureters

painted with 6 per cent phenol. The internal iliac vessels were exceedingly small, the arteries being not much larger than the inferior epigastric arteries. This was all the more remarkable seeing that she must have been about 7-weeks pregnant when the operation was done.

Third pregnancy. 11th September, 1957, patient found to be 16-weeks pregnant, Hb, 14·5 g. per cent. From then onwards she was seen weekly. Only 2 systolic readings exceeded 130, and the diastolic pressure exceeded 80 mm. Hg on only 4 occasions.

20th February, 1958, at 38 weeks, spontaneous labour, macerated male foetus, 3 pounds 2 ounces (1·4 kg.), small placenta.

Fourth pregnancy. Systolic B.P. only 5 times exceeded 120 mm. Hg before the 39th week.

22nd October, 1959, A.R.M. at term, female infant, 5 pounds 4 ounces (2·4 kg.), placenta normal size.*

By the age of 21 this petite woman had been delivered of 4 dead babies and one living healthy child. Her internal iliac vessels were incredibly small and denervation of them when the placenta was more than half formed prevented the onset of hypertension but did not save the foetus.

Case 12

Chemical denervation after the placenta was fully formed. Non-functioning left kidney.

Gravida-1, *aet*. 26, emergency admission 28th June, 1951, at 28 weeks. Rh negative, B.P. 190/100, P., 4 parts, O++, blood urea 40–65 mg. per cent, foetal heart muffled and very irregular.

3rd July, 1951, an extra-peritoneal incision was made through the left loin. The peritoneum was exposed as widely as possible, and the left common iliac artery and vein, the lower part of the abdominal aorta and inferior vena cava, and the left ureter were generously painted with 5 per cent phenol, while the exposed portion of the left lumbar sympathetic chain was coagulated by diathermy.

The patient made an excellent recovery from the operation. Between 4th July and 17th August the B.P. varied from 150–200/100–120, P., 2–9 parts.

18th August, 36 weeks, marked distension of gut, which commenced after operation and was present when she left hospital, B.P., 200/120, P., 6 parts, U., 90 ounces (2,557 ml.), blood urea, 55 mg. per cent. Foetus had not appeared to grow since operation although its heart beats had remained regular. Induction of premature labour.

19th August, 1951, female infant, 2 pounds 14 ounces (1·3 kg.), died shortly after delivery; numerous infarcts in small placenta.

October, 1952, I.V.P., non-functioning left kidney, right hydronephrosis and hydroureter. She attended badly and had become pregnant contrary to our advice.

Second pregnancy. L.M.P., 6th June, 1952. Seen weekly from 15th October. Admitted for rest and observation 4 times. Systolic B.P. only once exceeded 150, diastolic pressure persisted at about 80 mm. Hg, P., 1 part on one occasion only.

14th March, 1953, male infant 7 pounds 8 ounces (3·4 kg.). Postnatal visits, B.P. varied between 110–120/80–90, P., trace on one occasion.

Third pregnancy, 18th December, 1954, male infant, 7 pounds 4 ounces (3·3 kg.). The highest B.P., 155/110, occurred during the puerperium.

Fourth pregnancy. Apart from one reading of 160/100, B.P. varied from 130–150/80–100, P., nil, blood urea 25 mg. per cent.

1st December, 1956, spontaneous delivery at 38 weeks of female infant, 6 pounds 12 ounces (3·1 kg.).

Fifth pregnancy. Put on serpasil 1 mg., 4 times daily, at 28 weeks. B.P. varied from 120–140/70–90.

26th January, 1959, spontaneous onset of labour at 36 weeks, male infant, 6 pounds 4 ounces (2·8 kg.), which twice required exchange transfusion. Chemical denervation after the placenta was fully formed had no immediate good effect except perhaps to make the foetal heart regular. The patient refused to have her non-functioning left kidney removed.

Case 13

Failure of extensive pre-sacral neurectomy to benefit course of pregnancy.

16th April, 1951, gynaecological patient complaining of pain; right salpingo-oöphorectomy, extensive pre-sacral neurectomy.

25th June, 1952, psychiatrist diagnosed "hysteria" with poor prognosis.

1955, *aet*. 34, "pre-eclampsia", not in Bradford.

1957, "pre-eclampsia" at 26 weeks, B.P., 210/120, P., 2 parts, U., 11 ounces (313 ml.) blood urea, 25 mg. per cent.

29th January, 1957, death of foetus, induction of premature labour, foetus weighed 1 pound 8 ounces (0·7 kg.).

This patient subsequently returned to my care and on 9th June, 1958, denervation was performed, and the denervated vessels and exposed portions of ureters were painted with 6 per cent phenol. The left tube was patent but was thickened, indurated and pouting. B.P., 155/90. This patient has unexpectedly become pregnant again and her B.P. at present is 134/80 mm. Hg.† It is clear that extensive pre-sacral neurectomy prevented neither HP+ nor death of the foetus in her two previous pregnancies.

The above reported case notes, moreover, show that 5 of the patients who had successful pregnancies after the operation were over 30 at the time and 4 of them were over 35 years. A fall in B.P. was sometimes noted at the end of the first or beginning of the second trimester of pregnancy. In Case 6, for example, the blood

* Exactly one year later she gave birth to a second healthy daughter.

† The foetus died at about the 29th week without any rise in the maternal B.P.

pressure was 138/90 at 8 weeks and 100/60 at 12 weeks. Several hundred blood pressure readings were taken in these 14 patients (only those recorded by medical or senior nursing staff have been accepted). In the non-pregnant state values ranging from 112–160/72–100 were obtained in Case 7, from 110–140/70–90 in Case 8, and from 106–135/58–90 in Case 11. Wide variations in either direction were not uncommon during the antenatal period while in some pregnancies (Cases 6, 7 and 12) the highest blood pressure recordings were obtained during the puerperium. Likewise HP+ was not always associated with oliguria, for whereas Case 13 passed as little as 11 ounces (313 ml.), and Case 11, 14 ounces (398 ml.), Cases 7 and 8 respectively secreted 138 ounces (3,920 ml.), and 205 ounces (5,825 ml.), in 24 hours.

Nature's Experiment

Before discussing these results it might prove illuminating to contrast them with nature's exclusive and conclusive experiment (Theobald, 1956, p. 320). A saddle-shaped embolus occurred suddenly in a woman *aet.* 33, at about the 31st week of her sixth pregnancy. It obliterated the femoral pulse on both sides and prevented her from taking more than a few steps at a time. The pregnancy nevertheless continued and the woman, who showed no sign of "toxaemia", gave birth at term to a healthy infant weighing 6 pounds 1 ounce (2·8 kg.), which throve. Professor Patrick Fitzgerald, of Dublin, successfully removed this embolus some eight weeks after it had occurred and I am greatly indebted to him for allowing me to report this unique and unequivocal case and for providing the illustrations (Figs. 4, 5). The mother who is alive and well is a tribute to his skill.

It is clear that the embolus, which extended downwards well into the femoral artery on each side, virtually blocked both internal iliac arteries. Both the foetus and the maternal legs were kept alive by blood from the ovarian arteries, together with that which may have been provided by anastomotic branches of gluteal arteries communicating with the distal portions of the internal iliac arteries.

Discussion

Rough estimates of the total uterine blood flow in human pregnancy at term vary between 500 and 700 ml. a minute and it is thought that both the blood flow and oxygen consumption remain constant throughout gestation, provided they are calculated on the basis of unit weight of pregnant uterus (Browne and Veall, 1953; Morris *et al.*, 1955, 1956; Assali *et al.*, 1960). It has been shown that if the "pipe line"* (the sum of the cross sections of the uterine and ovarian arteries) is below a critical size the placenta will be small, the foetus will be small and die *in utero*, and the mother will have HP+ before the 30th week, and that this sequence of events will recur in subsequent pregnancies. The degree of diminution of the pipe line is evidenced clinically by the size of the infant and the stage of pregnancy at which HP first occurs. The worse the placenta the earlier is the onset of HP. The pipe line may be reduced either by generalized arterial spasm or because of hypoplasia of the arterial tree. Hypertension, unless it exceeds a certain level, does not interfere with placentation and consequently does not affect the weight of the baby (Theobald, 1956, p. 172; Dodds, 1958).

Denervation throws light on obstetric problems, but is not often indicated, for while adequate antenatal care may not prevent the onset of H, it can usually ensure a favourable issue for both mother and child. It may be worth doing in an additional small number of women whose blood pressure is relatively normal in the non-pregnant state, but who are obliged to spend long periods in the antenatal ward because of recurrent H and HP. Arteriograms could help in selecting suitable patients and the mere painting of the internal iliac vessels with 6 per cent phenol might suffice, and thus reduce the severity of the operation.

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* Flow of liquid through a tube varies with the fourth power of its diameter so that $F=K\ (d_1^4+d_2^4)$ where F=blood flow to uterus, d_1 the diameter of the uterine, and d_2 that of the ovarian arteries. It also varies with such factors as the length of the arteries and the blood viscosity, so that $F=\frac{P}{R}$, where P is the pressure and R the resistance.

It seems evident that on the one hand denervation done after the placenta is partly or completely formed does not save the foetus (although it may prevent the onset of hypertension, Case 11), whereas on the other a saddle-shaped embolus which occurred at the 31st week neither interfered with foetal growth nor caused maternal HP. These facts underline the importance of actual placental formation (which includes not only concepts of size and physical structure but also of enzymes and adequate transport systems) and show that a well-formed placenta can withstand severe deprivation without harm to the foetus (see Browne and Veall, 1953).

These views receive indirect support from antenatal observations. Over the past 12 years I have been personally responsible for some 4,500 patients with H, of whom roughly 1,000 also had P. HP starting before the 32nd week was almost invariably associated with a small placenta and an unduly small foetus and in these patients H almost invariably recurred in subsequent pregnancies. Conversely no woman who had eclampsia after the 39th week of her first pregnancy (whose blood pressure had remained normal until within a week of the attack) had H in subsequently observed pregnancies.

It is proposed briefly to pursue two lines of conjecture opened up by the above evidence, the first concerning the different types of eclampsia, and the second the light that pregnancy may throw on hypertension.

The Different Types of Eclampsia

It has been postulated that a small pipe line is inevitably associated with a small foetus, whereas eclampsia at term may be associated with the birth of a living infant weighing over 10 pounds (4·6 kg.). Eclampsia and HPOUS may therefore conveniently be divided into two main groups according as to whether they occur in association with an inadequate or a well-formed placenta. The concept of placental ischaemia is largely due to Ernest Page, but those who follow him regard it as being strictly comparable with renal ischaemia, neither do they stress the significance of the actual formation of the placenta. The concept here advocated relates the phenomena to nutrition, and the term atelsitesis* will be used, not for imputed reasons, but tentatively, and merely to simplify concepts which can be tested against clinical observations.

(1) *Eclampsia and HPOUS Occurring in Association with a Small Badly-formed Placenta*

(a) *Primary placental atelsiteses* are inevitable, recurrent, and invariably associated with a small placenta and a small foetus. The smaller the pipe line the earlier the onset of HP.

(b) *Secondary placental atelsiteses* follow the same sequence as the primary variety. They are due to qualitative, not quantitative, deficiencies in the blood passing through the pipe line, and can therefore be prevented. The primary variety occurs notwithstanding a perfect maternal diet, whereas the secondary type is caused by inadequate maternal nutrition. These two types are not necessarily distinct and often merge.

(2) *Eclampsia and HPOUS Occurring in Association with a Well-formed Placenta*

Maternal atelsiteses. The maternal diet may be either inadequate or imperfectly assimilated or it may cause overweight. Such defects may not interfere with placentation and may not operate until the end of pregnancy. Infarcts and disease may affect both ill-constructed and well-formed placentas (Scott, 1958; Dockery, 1960). Primary placental atelsiteses are more common in centres where the antenatal care is adequate whereas maternal atelsiteses form the higher proportion of cases in backward countries, and are relatively easily preventible.

Some Factors Concerned with Hypertension

It has been reported above that denervation of the internal iliac vessels may either prevent the occurrence of H or lessen its degree. It is accepted that a fall of blood pressure commonly occurs towards the end of the first or the

* The word previously suggested was atelositesis. The letter "o" has been omitted and the word is pronounced a-tell-sight-esis (eses) to scan with atelectasis. It means "imperfect nutrition".

beginning of the second trimester of pregnancy. Then too, each year between six and seven thousand pregnant women in England and Wales are found to have a raised blood pressure (essential hypertension) which persists throughout pregnancy, the puerperium, and usually throughout life. A further 60 to 70 thousand apparently normotensive women acquire H≧140/90 mm. Hg during the latter half of pregnancy, of whom 3,000 also develop proteinuria. In these women the blood pressure returns to normal during, or soon after, the puerperium, but hypertension recurs in later life in 10± per cent of them, becomes permanent, and seriously contributes to mortality (Gibson, 1921; Caldwell and Lyle, 1921; Gibberd, 1931; Young *et al.*, 1932; Bechgaard *et al.*, 1956, 1958). It was at first thought that pregnancy "toxaemia" itself either caused chronic nephritis or hypertension, but later studies cast doubts on this assumption (Theobald, 1933; Isenhour *et al.*, 1942; Barnes and Browne, 1945; Humerfelt and Wedervang, 1957). It was therefore postulated (Theobald, 1936) that the defects preceded the pregnancy and that "the inborn errors of metabolism which eventually cause hypertension are revealed by pregnancy", and this view has been widely accepted (Browne, 1939, p. 341; Tillman, 1955).

The essence of pregnancy is the introduction into a woman of a parasitic foetus and a very large endocrine gland, while the placental circulation introduces what is in effect an arterio-venous shunt. No stigmata can be discovered in these women before or after pregnancy, and they are only temporarily revealed by a physiological process which strains the homeostatic mechanisms. There are two current views concerning the nature of essential hypertension. The first regards it as a disease entity and presumes two separate populations, the one in which the blood pressure rises significantly in middle age and the other in which it does not (Morrison and Morris, 1959; Platt, 1959). The second recognizes no arbitrary dividing line between normal and abnormal blood pressures, and assumes hypertension to represent a quantitative rather than a qualitative deviation from the norm (Oldham *et al.*, 1960). The evidence presented in this paper suggests that women who develop hypertension between the 20th and 34th weeks of their first pregnancy had defects which preceded conception, will have recurrent "toxaemia", and essential hypertension in middle age (Bechgaard *et al.*, 1956, 1958), and thus supports the view that essential hypertension is a distinct entity. It is suggested that nutrition may be the key, the endocrine system the lock and rauwolfia a clue.

Conclusions

The main purpose of this paper has been to describe the inevitable sequence of events in pregnancy associated with a grossly small pipe line and to show that in selected cases this sequence can be prevented by denervation of the internal iliac vessels. It is suggested that patients with HP+ can be divided into two main groups according as to whether the signs and symptoms are associated with an inadequate or a well-formed placenta. There are clearly many degrees of primary placental inadequacy, which can be determined clinically by the size of the foetus and the stage of pregnancy at which HP starts. Seeing that blood pressure is a measuring rod used more frequently by the obstetrician than by any other member of the profession, he should be in the position to make a unique contribution to the study of hypertension. He alone can predict that a woman with a normal blood pressure and no detectable stigmata, will most probably suffer from hypertension in middle age which will seriously contribute to her death.

Renal biopsy has made it possible to state that nephropathy may be due to more than 30 different disease states, and physicians, while not actually discarding the term "Bright's disease", have dissected it into many patterns which they do not hesitate to modify as knowledge advances. Obstetricians by attention to nutrition and by using bed rest and hypotensive drugs, have learned how to eliminate eclampsia, and virtually to eliminate the toll of maternal and foetal wastage associated with HPOUS. Their retention, in the name of tradition, of misleading terms such as "toxaemia" and "pre-eclampsia" may, however, obfuscate the fascinating kaleidoscopic patterns associated with aberrant pregnancy,

and prevent them from making their rightful contribution to medicine. For pregnancy is in very truth a crystal into which the obstetrician can gaze and foresee the course of future pregnancies and the fate which is likely to encompass certain women providing they live long enough to embrace it.

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INTRA-UTERINE ISOTOPES IN MENORRHAGIA

BY

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SOME women complain bitterly if menstruation lasts a day more than their usual 3 or 4 days; others apparently tolerate heavy bleeding for months without complaint. Without attempting an exact definition of menorrhagia, a typical clinical history of a patient selected for intra-uterine isotope treatment goes as follows: menstrual bleeding was severe enough to merit admission to hospital without delay: careful anamnesis (especially with an eye to domestic anxiety or overwork at home or factory) preceded assessment in the ward and theatre with the object of excluding co-existent disease such as fibroids or endometriosis. When curettings were reported non-malignant (perhaps cystic glandular hyperplasia) we gave the patient reassurance that she had "no serious disease", i.e., in the parlance of the Midlands, cancer was excluded. With this reassurance she was discharged from hospital but advised to lead a leisurely life; if domestic or factory work made this difficult or impossible a visit of two weeks to a hospital convalescent home was never difficult to arrange. In our experience this combination of rest, reassurance and curettage gives a high spontaneous cure rate in women aged 40 to 50, provided that they suffer only from simple menorrhagia. If, however, menorrhagia persists it is our practice to consider hysterectomy, or very rarely (e.g., if the patient is unfit for surgery), radium or X-ray castration.

The object of this clinical trial of radioactive isotopes was to assay the effectiveness of endometrial cautery by isotopes with the objective of reducing the number of patients who were compelled by menorrhagia to submit to hysterectomy. The idea of burning the endometrium is not new. For example, Ten Berge, writing in 1936 from Holland on the use of a thermostatically-controlled uterine diathermy, states that German workers had actually experimented with intra-uterine steam! This, of course, was before the turn of the century and Röntgen therapy. In the field of gastric surgery in more recent years, Simon (1949) commenced experiments with radioactive phosphorus in an attempt to lower the gastric acidity of dogs, and Douglas and his colleagues (1950) reported further animal studies. Douglas observed that Beta irradiation of the stomach of a dog destroyed much of the gastric mucosa but the rate of regeneration, and therefore the permanent effect in cutting down function, was not clear from his experiments. The same problem was present in our initial experimental work both in animals and in the human (McLaren, Heath and Quinton, 1953). In none of our experiments was the 2 to 3 mm. cautery-effect by radioactive phosphorus effective in removing permanently the vaginal epithelium of a rabbit; correspondingly in the human, endometrial regeneration was also the rule after intra-uterine irradiation so that within 2 or 3 months of isotope treatment there was little evidence of isotopic burning.

Following Simon (1949) and Douglas *et al.* (1950) who distended the stomach of dogs in their experiments, we attempted to distend the uterus with a balloon to open up the whole area of the endometrium to a central rod containing radioactive phosphorus. It proved to be extremely difficult, however, even with the cervix stitched to enclose the balloon, for the latter still tended to bulge down the cervical canal

under the considerable pressure required to distend the uterus. Finally, we found that a simple rod-shaped applicator designed by my co-worker J. C. Heath, formerly of the Department of Physics, University of Birmingham, was easy to handle in the theatre or ward (Fig. 1). It carried radioactive phosphorus in a sheath of perspex and although, considering the shape of the uterine cavity, it could not be expected to irradiate all the endometrium, most of the surface endometrium (except at the cornua) was irradiated by *B* rays (McLaren, Heath and Quinton, 1953).

P^{32} applicators have to be made up frequently on account of their rapid rate of decay and involve a certain amount of exposure to Beta irradiation during preparation so that we proceeded to assay $Cerium^{144}$. This also proved unsatisfactory since the applicator tended to embed itself in the uterus; it was therefore abandoned for $Strontium^{90}$ with the convenient half life of 20 years. This applicator enclosed radioactive Strontium in German silver and was made by A. Quinton, formerly physicist to the Department of Radiotherapy at the Queen Elizabeth Hospital. In the hands of a gynaecologist or experienced junior it proved to be safe and easy to use without risk of leakage due to the perspex cracking, a theoretical disadvantage of the P^{32} applicator. No special precautions to protect the patient or nursing staff were necessary with the ensheathed Sr^{90} applicator (Fig. 2), although with P^{32} all dressings were checked for radio-activity. Apart from one occasion when the Sr^{90} applicator slipped down the cervical canal to burn the upper vagina there were no accidents, so that with increasing confidence patients were allowed out of bed even without a suture in the cervix to enclose the applicator.

Case Selection

The total number of patients with uncomplicated menorrhagia in the 4th decade of life who present in the course of a year in our hospital is not great and of these there were few who met our criteria for Beta therapy. These criteria can be summarized as follows: if our normal routine of uterine curettage and rest (and perhaps more important reassurance that no serious disease was present) left the patient seriously disabled by menorrhagia so that hysterectomy seemed inevitable, isotope treatment was offered as an alternative to surgery. A full explanation of the purpose and the prospect of a cure by the isotope method was given and time left for the patient to think it over and confer with her husband. We guessed from our pilot experiments that not more than 60 per cent of patients with recurrent menorrhagia would respond successfully so that we made no attempt to persuade them to accept isotope therapy; on the contrary we made it clear that a cure could not be promised. Moreover, where doubt existed on the clinical findings, e.g., if the history and findings suggested endometriosis or old inflammatory disease, hysterectomy was preferred. With these standards, in our unit of 32 gynaecological beds our numbers were necessarily small and were further limited by the need of many of our patients to be guaranteed a cure which isotope therapy could not offer.

Clinical Experience

Re-admission to hospital for recurrent bleeding permitted a complete re-assessment of the clinical facts and a second curettage prior to insertion of the rod-shaped applicator. If the applicator was not firmly held by the uterine cavity we inserted one or two stitches to close the cervical canal, but this was seldom necessary. No packs were used and the patient was allowed out of bed with the applicator *in utero* as soon as she recovered from the anaesthetic. When $Cerium^{144}$ was used, in 3 out of 7 patients with the applicator *in situ* for 3 or more days, it became embedded in the endometrium so that with the sealing-off effect of oedema of the upper cervix, hysterectomy became necessary to remove the applicator. Apart from these 3 cases, however, there was no difficulty with other isotopes, the applicator being removed in the ward by the house surgeon. One patient, already mentioned, had an obvious vaginal burn when the lower end of the applicator was found at removal to have slipped out of the cervical canal. Although our

FIG. 1

Phosphorus[32] applicator enclosed in a sheath of perspex *in situ*. Note the tiny intramural fibroid.

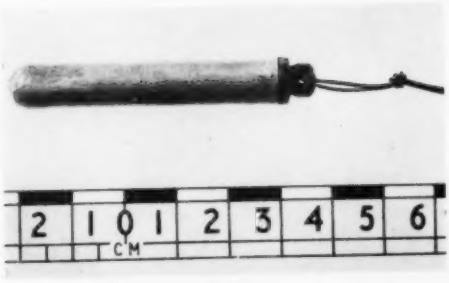

FIG. 2

Strontium[90] applicator encased in German silver sheath (*vide* appendix for dose rate at various depths).

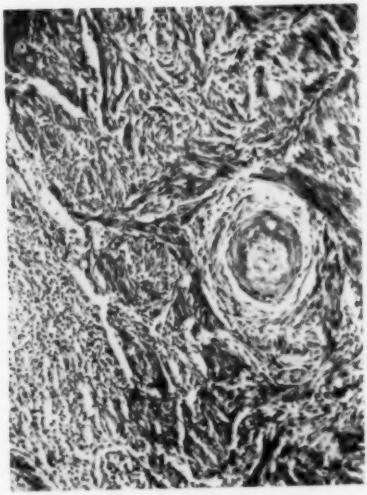

FIG. 3

Deep to surface burn marked vascular thrombosis and stromal fibrosis.

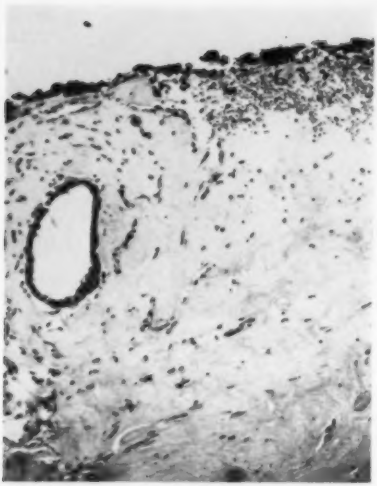

FIG. 4

Hyaline "burn membrane" penetrated by an endometrial gland. The surface endometrium has almost covered the area of hyalinization.

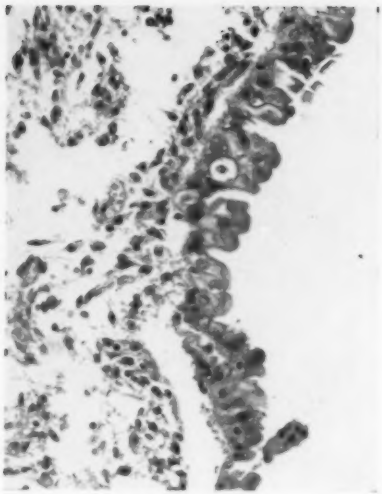

FIG. 5

Distorted endometrial cells lining the uterine cavity 3 months after P^{32} burn.

FIG. 6

After Sr^{90} had failed to control menorrhagia this uterus was removed with the only remaining adnexa. Note intramural fibroid and old inflammatory disease of the tube and ovary.

H.C.McL.

uterine dosage calculation became a guess the patient continued satisfactorily, the vagina healed rapidly and within a year she reached the menopause without further menorrhagia.

With the isotope *in utero* the patient felt no sickness or other unpleasant sensation. Hot flushes and sweating were not produced immediately or later, or if present before treatment they were not exaggerated in quality or frequency. Allowed up soon after the anaesthetic the patient could proceed home immediately after removal of the applicator. A pink discharge was occasionally noted for a week or two but this was transient and did not constitute a disadvantage to the method.

Results

Total subjected to Beta therapy=52.

A. *Pilot Assay of P^{32} (12 cases)*

In this trial, hysterectomy was planned at 3 months or earlier if bleeding continued unabated: thus follow-up was inadequate for complete clinical assessment.

Results:

Total number of patients	12
Normal menses or no period after P^{32}	8
Failure (persistent haemorrhage and hysterectomy)	4

B. *Clinical Trial with Adequate Follow-up*

Isotope P^{32}	6	40
Isotope Ce^{144}	7	
Isotope Sr^{90}	27	

Cure Rate:

Isotope P^{32} ..	6 =	3
Isotope Ce^{144} ..	7 =	0
Isotope Sr^{90} ..	27 =	13
Total	=	16 (40%)

If we exclude $Cerium^{144}$ with its tendency to embed in the endometrium, the cure rate is raised to 48·5 per cent, viz., of 33 patients subjected to Beta irradiation from P^{32} and Sr^{90}, 16 were cured. The period of follow-up of 16 successful cases extended to 1 year, 1; 2 years, 5; 3 years, 2; 4 years, 1; 6 years, 1; the remaining 6 reached the menopause soon after isotope therapy and with no symptoms of importance.

Comment on Our Failures

We published in our initial report a detailed description of the "burns" produced by Beta irradiation (McLaren *et al.*, 1953). Further specimens continued to show the remarkable regeneration of the endometrium which follows isotope burning. Our initial animal studies using P^{32} were not repeated for $Cerium^{144}$ or $Strontium^{90}$, but these isotopes all released about 250,000 r.e.p. per treatment at the surface and produced necrosis of the endometrium of the human uterus to a depth of 2 to 3 mm., i.e., the burn from $Strontium^{90}$ and $Cerium^{144}$ is comparable to that produced by P^{32}. Histology showed that, below the initial surface necrosis, marked oedema and later marked vascular thrombosis was apparent (Fig. 3). The healing process commenced quickly so that after 3 months a more or less thick endometrial covering was laid down to cover evidence of deeper irradiation damage in the form of a stromal hyaline membrane. This waxy tissue almost free from endometrial glands we have called a "burn" membrane (Fig. 4). In our initial 11 specimens removed 3 months after P^{32} treatment, 4 showed this condition in the stroma and a further case showed hyaline effects after only 2 months; a total of 5 out of 12. The lining endometrium as it recovered showed evidence of dysplasia (Fig. 5) but in the specimens examined after 6 months or more the endometrium had recovered and in some there was a full luteal (pre-menstrual) phase of development. Ovarian studies both macroscopic and microscopic suggested undisturbed function, viz., corpora lutea or Graafian follicles with no evidence of tissue damage. This we should expect with the small doses of gamma irradiation reaching the ovaries as a result of *Bremsstrahlung* or secondary gamma irradiation (Appendix A).

In our clinical assessment we did our utmost to exclude pelvic pathology (fibroids, old inflammatory disease, endometriosis) but we used only simple clinical methods, viz., a careful history, examination with and without general anaesthesia. A careful curettage was also routine with a search with forceps for endometrial polyps. In order to allow as deep a penetration of the endometrium as possible curettage preceded the insertion of the isotope-

applicator. Although we treated one known and one suspected case of endometriosis our policy was to exclude all except patients with uncomplicated menorrhagia who had failed to respond to our usual conservative routine of curettage and rest.

Surgery After B Irradiation

We have already mentioned 3 technical failures due to embedding of a Ce^{144} applicator with oedematous closure of the endocervix after 3 to 4 days *in utero*; hysterectomy was obligatory to remove the applicator.

A further 3 patients with persistent bleeding following unsuccessful Beta irradiation were deemed unfit for surgery; the menopause was induced by radium in 2 and X-rays in 1. In 9 post-isotope hysterectomy specimens although regenerating endometrium was observed no gross pathology was detected by naked eye or on histological examination, but finally at hysterectomy in 7 specimens we were able to show small intramural fibroids (Fig. 6). This, of course, does not mean that we should consider these fibroids to be *per se* a cause for further bleeding. In summary:

Technical failure (Ce^{144} plugged *in utero*)	3
"No pathology" in specimen	9
No histology (treated by X-rays, 1; radium 3)	3

Pathology of Uncertain Relevance to Bleeding in 12 Specimens (Fig. 6)

Fibroids (up to hazelnut size; intramural)	7
Adherent ovaries	3
Endometriosis (known before *B* therapy)	2

Discussion

Since it was dissatisfaction with the accepted methods of treating menorrhagia which encouraged us to explore isotopic cautery it is perhaps justifiable to make a short commentary on menorrhagia as a therapeutic problem.

What methods are open to the clinician in the cure of a patient with simple menorrhagia in the 40–50 age group? First of all, after curettage has excluded carcinoma, he may play for time and a spontaneous remission or cure. The spontaneous cure rate is high in the 40's and even higher if she is 50 or over, so high that one is almost obliged to recommend conservative therapy as a first step (Foulkes, 1949; Macgregor and Noble, 1953). If, however, recurrent or persistent simple haemorrhage makes more radical treatment obligatory it must not be forgotten that, even in the most competent hands, hysterectomy still carries a small but definite morbidity, for example, from embolus or even, on rare occasions, a slipped pedicle. On the other hand, a cure is certain and with ovarian conservation our observations show that we may expect the menopause to be relatively free from disturbing symptoms.

As an alternative to surgery for menorrhagia some clinicians still use radium or X-ray castration. Certainly castration whether by gamma or X-rays is effective in the cure of bleeding and it is safe. Our own observations showed clearly, however, that unpleasant symptoms are very common after radio-castration and perhaps the most startling to the patient is the sudden onset of sexual anaesthesia; three other important sequelae are hot flushes, sweats and the development of senile changes in the genital tract; and it is important to note that the changes in the genital tract are premature and that hot flushes may present for months or years (McLaren, 1950). We therefore reserve castration for the very occasional patient unfit for hysterectomy. We should not prescribe it for a woman with an interest in the sexual side of her married life or indeed for any younger woman. We are not able to comment from extensive experience with hormone therapy in the permanent cure of simple menorrhagia in the age group 40–50. Except to establish temporary control of excessive bleeding (for example, until a patient can be admitted to hospital and transfused) it is not our practice to prescribe hormones for menorrhagia although, of course, one must attempt control in younger women tiding them over in the hope of a conception or a remission. In summary, then, surgery carries a slight risk, radio-castration the prospect of severe menopausal symptoms, while hormone therapy in the age group 40–50 has in our belief only a limited place.

Isotopes as an Alternative

As far as we can ascertain the first mention of isotope technique in the literature was a short essay written in 1950 in which Franco Crainz, of Novarro, Italy, discussed the possibility of using *B* rays in metrorrhagia. The stimulus to assay isotopes in our unit came from discussions with Glucksmann of the Strangeways Laboratories, Cambridge, before this date; he knew of our dissatisfaction with radium-castration and surgery in the therapy of simple menorrhagia and it was with his encouragement and with support from the Medical Research Council that we decided to explore P^{32} as a therapeutic endometrial cautery. When we consider how many factors may be operative in simple menorrhagia such as anxiety or overwork, any attempt to explain how endometrial cautery achieves its haemostatic effect is bound to be incomplete (Blaikley, 1949). For instance, it was obvious at the outset of our experimental studies that cauterization of an "end-organ" (the uterus) could do little to alter the vascular changes in the pelvis brought about by menstruation, indeed the burn itself initially led to obvious local vasodilatation.

The object of attempting a temporary or permanent removal of endometrium was based on the theory that an acellular or perhaps less vascular uterine lining might react less to hormonic stimulation providing a temporary diminution in menstrual loss. This phase it was hoped might allow resumption of normal menses or better, the arrival of the menopause with intact ovaries. Our attempts at permanent removal of endometrium failed although in some specimens a waxy avascular layer developed in the endometrial stroma. Although fibrosis and capillary thrombosis was also marked (Fig. 3) it is doubtful if we achieved a diminished vascularity by burning with isotopes. Regeneration of endometrium was the rule within 3 or 4 months, i.e., the local effect of burning was temporary.

Finally, what has isotopic therapy to offer to women of 40 with uncomplicated menorrhagia? Is a 50 per cent chance of a cure without surgery a reasonable therapeutic proposal? Our practice was based on our initial pilot experiment where about half of our patients avoided hysterectomy after P^{32}. We made no attempt to persuade patients to accept isotopes and quite naturally the busy housewife or professional woman usually opted for surgery. After the annoyance and debility of menorrhagia the 14 days in hospital and 2 or 3 months before full duties, seemed to this group to be a reasonable price for the certainty of a cure. It may be, however, that in other parts of the world patients may prefer to accept isotopic therapy as a conservative method. I have in mind, for instance, our West Indians who often show a remarkable resistance to proposed hysterectomy and I believe French women also tend to choose conservative therapy if offered a choice.

The method is certainly worthy of further trial provided careful selection is agreed and this should take advantage of an initial curettage to exclude carcinoma of the corpus while offering the chance of a spontaneous cure without surgery or isotopes.

Finally, is this second curettage and cautery of the endometrium by Sr^{90} any more effective than a second curettage? There seems to be no easy way to answer this question either from the literature or from our experience in Birmingham. To get an answer we should have to try to pair patients submitted to a second curettage with those subjected to repeat curettage with added Beta irradiation, correlating age, severity or bleeding, pelvic findings and so on. We should also require adequate time for follow-up. Without this the question must remain unanswered.

Summary

(1) Simple recurrent menorrhagia in the 4th decade of life is usually treated in our unit by hysterectomy with ovarian conservation; Sr^{90} offers an alternative although it offers a cure rate of about 50 per cent.

(2) Following a pilot experiment using P^{32} as an endometrial cautery with only a 3-month follow-up before hysterectomy we now report a further 33 patients with recurrent menorrhagia following curettage who were considered severe enough to require hysterectomy. Intra-uterine isotopes (P^{32}, Sr^{90}) cured 16 of whom 6 reached the menopause.

(3) The method appears to have a small but definite place among the therapeutic methods available for simple menorrhagia; it is recommended only after failure of conservative therapy.

Acknowledgments

The isotope applicators were designed by J. C. Heath and A. Quinton and I wish to acknowledge with gratitude their help in this study. My thanks are also due to Messrs. R. F. Farr and H. Besford of the Department of Radiotherapy, of the Queen Elizabeth Hospital. I also wish to thank T. F. Dee, Department of Clinical Photography and Miss M. E. Attwood, University Research Assistant, for the histological preparations.

For encouragement to carry out this study and for supplies of isotopes we wish to acknowledge our debt to the Medical Research Council.

Finally, I wish to thank my colleagues in the Midlands who referred patients for this trial of therapy.

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Appendix A

Bremsstrahlung from B rays.
Source to ovary:

Distance cm.	3	4	5	6	7	8
Dose (r)	7	4	3	2	1·5	1

These small doses may be compared with the doses provided by the natural background of 0·1 r per year of life, and, say, 0·1 per annum from diagnostic radiology both considered to be gentically significant doses.

With *B* irradiation of the uterus, however, the dose of gamma irradiation of the ovary must be weighted to obtain the genetically significant dose.

(*a*) By sharing the ovarian dose (say 2 to 3 r) given to our patient among the class or group of female patients liable to be treated by *B* irradiation.

(*b*) By weighing the dose for any reduction of child-expectancy produced by treatment.

Thus:

Genetically significant dose per annum
= dose delivered to the ovaries by this treatment
× the fraction of the female population of child-bearing age so treated each year
× *child expectancy of these women*
child expectancy of women of the same age in the population at large.

The result will obviously be quite small and is to be compared with the following genetically significant doses:

Natural background 0·1 r per annum
Diagnostic radiology 0·1 r per annum approx.

Similarly, one could compare the genetically significant dose from this treatment with that from "conventional" X or gamma ray A.M. as:

$$\frac{\text{Dose delivered to ovaries by method 1}}{\text{Dose delivered to ovaries by method 2}} \times \frac{\text{Child expectancy subsequent to method 1}}{\text{Child expectancy subsequent to method 2}}$$

Now the number of patients selected for treatment in our clinic over a period of some 8 years is no more than 50 and they are not for the most part in the reproductive years so that the result (genetically significant dose per annum) is very small indeed. From the point of view of heredity, therefore, there would seem to be no reason for discontinuing our trial of Sr^{90}, although to be almost clear of the possibility of a genetic contribution of gamma irradiation (Bremsstrahlung) the method might best be confined to the 40-plus age group when the prospect of conception is very low.

Appendix B

Statement of Cylindrical Strontium Applicator

by

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Loading	46 mc. 3·0 mm./2 cm.	} on the 30th June, 1954.
Half-life	19·9 years.	
Radiation	The Strontium^{90} is in equilibrium with the daughter isotope yttrium^{90}, half life 61 hours. *Radiation from strontium*—Beta particle Emax—0·61 Mev. *Radiation from yttrium*—Beta particle Emax—2·18 Mev. There is no primary gamma radiation.	
Dimensions	Overall length	5·8 cm.
	Active length	5·0 cm.
	Overall diameter	1·05 cm.
	Active diameter	0·90 cm.
	Inside former diameter	0·60 cm.
	Effective active diameter	0·8 cm.

Penetration of Radiation

Experimental measurement from flat source

0	1	2	3	4	5	10	mm.
100	70	57	42	30	20	1·3	%

Estimated measurement for cylindrical source

0	1	2	3	4	5	10	mm.
100	62	46	31	20	12	8	%

Surface Dosage

Experimental measurement (comparison with flat plaque) 80 r/min.

Theoretical Estimate (many assumptions) 110 r/min.

Comparison with P^{32} Applicator (McLaren, Heath, Quinton, 1953).

Dose rate at various depths:

0	1	2	3	4	5	10	mm.
80	50	37	25	16	9·6	6·4	r/min.
4,800	3,000	2,200	1,500	960	576	384	r/min.

Treatment time

Based on P^{32} treatments 12 hours

Based on dose Suggest 15,000 at 3 mm.
Treatment time 10 hours.

Replacement of Perspex sheath for German silver

Direct measurements by H. Besford, Physicist to the United Birmingham Hospitals showed a reduction in surface dose rate from 80 r/min. to 28. This was allowed for in the duration of intracautery treatment (about 30 hours).

PSEUDOMYXOMA PERITONEI

BY

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PSEUDOMYXOMA peritonei is defined by Willis (1952) as a condition of massive gelatinous accumulation in the peritoneal cavity and gelatinous infiltration of the subserous tissues resulting from perforation of pseudomucinous cystomas of the ovary. Although pseudomyxoma peritonei is usually of ovarian origin a similar condition results from intra-peritoneal spill of the contents of a mucocele of the appendix. The peritoneal involvement secondary to mucoid adenocarcinomas of the intestine and stomach may be indistinguishable from pseudomyxoma of ovarian origin.

In a recent paper Malpas (1959) has suggested that pseudomyxoma peritonei of ovarian origin is always a malignant condition and that the common benign pseudomucinous cyst is not causally related. Our experience of the disease has not been in accord with the observations of Malpas and this has prompted the presentation of our findings.

HISTORICAL NOTE

With the advent of ovariotomy as an established procedure in the treatment of ovarian cysts, surgeons began to recognize the naked eye appearance of pseudomyxoma peritonei. Spencer Wells (1865) in England and Péan (1880) in France, amongst others, failed to make a distinction between pseudomyxoma and colloid carcinomatosis of the peritoneum. Subsequently pseudomyxoma peritonei was established as a disease entity associated with ruptured ovarian cysts but the pathology was still confused. Schröder (1874) spoke of the "infectiousness" for the peritoneum of the perforated "cystoma myxomatosa", and to Virchow is ascribed the interpretation that the disease was a "peritonitis myxomatosa". The use of these descriptive terms indicates a belief that the gelatinous effusion was a result of myxomatous degeneration of the connective tissues of the cyst wall and of the peritoneum and that the lining secretory epithelium of the ovarian cyst as the source of the peritoneal effusion was not recognized. Werth, in 1884, first pointed out the causal connexion and suggested that the affection of the peritoneum was not a primary lesion, but the result of an inflammatory reaction to a "foreign body" formed by the gelatinous ovarian contents discharged into the abdominal cavity. He renamed the disease pseudomyxoma peritonei to distinguish the essentially epithelial lesion from that of connective tissue origin. Frankel in 1901 was first to describe the disease in the male as a complication of a ruptured mucocele of the appendix.

In 1912 Professor Thomas Wilson presented an outstanding paper on the subject to the obstetric and gynaecological section of the Royal Society of Medicine. It was based on the meticulous records of 6 cases on which he had operated in the General Hospital, Birmingham.

MATERIAL

The records of 13 cases of pseudomyxoma peritonei admitted to the Women's Hospital, Birmingham, during the years 1950–59 have been reviewed; 12 cases were of ovarian origin and 1 the result of rupture of a mucocele of the appendix. The subsequent history of all but

one of the cases has been traced and the living patients have been followed up. The pathological material has been re-examined.

Incidence

During the same decade a total of 337 patients with benign and malignant pseudomucinous tumours of the ovary were operated on, giving an overall incidence of 3·5 per cent for this complication. This is a much lower incidence than that reported by von Nagy (1933). He had 10 cases of pseudomyxoma in a series of 122 pseudomucinous tumours, an incidence of 8·1 per cent. In 272 of our patients the lesion was a cystadenoma and pseudomyxoma was found as a complication on 10 occasions. This incidence of 3·6 per cent compares with the 4·2 per cent reported by Wilson (1912) in his series of 144 cases of pseudomucinous cystadenomata.

Pseudomyxoma peritonei is relatively rare and the recent literature studied contains reports of single or several cases. The only large series are those collected in the Mayo Clinic between 1912 and 1954; Masson and Hamrick (1930) reported the first 30 cases and by 1954 Cariker and Dockerty (1954) were able to add a further 14.

Clinical Analysis

The clinical features of the 12 cases of ovarian origin are tabulated (Table I); 11 conform to the classical description of the disease and one is atypical.

The greatest number (6) were in patients in the 6th decade. All but 2 were married and, of the 10 married women, 8 were parous.

Four patients had a relevant surgical history. Two had 3 laparotomies for pseudomyxoma peritonei. Mrs. S. (Case 2), aged 35, had her

Table I

Clinical Résumé of Cases Associated With Pseudomucinous Cysts

Case No.	Age	Parity	Previous Surgical Treatment	Duration of Abdominal Enlargement	Presenting Signs in Abdomen	Findings at Laparotomy
1	50	2	None	5 months	Free fluid	Loose jelly. Ruptured cyst of left ovary and right ovary covered by adherent jelly. Appendix also covered by jelly
2	35	1	(*a*) Total hysterectomy and bilateral salpingectomy for pseudomyxoma 20 months before and *(*b*) Laparotomy for recurrence 4 months before admission	2 months	Tumour	Free and loculated jelly in the peritoneal cavity and widespread gelatinous nodules. No comment on appendix
3	40	1	None	3 months	Tumour and free fluid	Loose jelly. Unruptured cyst of left ovary, right ovary normal and adherent jelly on tubes. Mucocele of appendix with intact wall
4	66	0	Right salpingo-oöphorectomy for a pseudomucinous cyst 28 months prior to admission†	3 months	Free fluid	Free and loculated jelly in the peritoneal cavity and widespread gelatinous nodules. Ruptured cyst of left ovary.‡ No comment on appendix

* For details see text. † For details see text.

‡ Microscopic examination revealed a cystadenocarcinoma.

TABLE I—*continued*

Case No.	Age	Parity	Previous Surgical Treatment	Duration of Abdominal Enlargement	Presenting Signs in Abdomen	Findings at Laparotomy
5	44	2	None	2 months	Tumour	Loose jelly and gelatinous nodules on the omentum. Unruptured cyst of left ovary, adherent jelly on right ovary. Ruptured mucocele of appendix
6	54	0	None	3 months	Tumour and free fluid	Loose jelly and widespread gelatinous nodules. Ruptured cyst of right ovary† and left ovary covered by adherent jelly. Appendix also covered by jelly
7	57	6	*Total hysterectomy and bilateral salpingo-oöphorectomy and appendicectomy for pseudomyxoma 12 years before admission	4 months	Free fluid	Loculated jelly in the peritoneal cavity
8	66	1	None	2 months	Tumour	Loose jelly. Ruptured cyst of left ovary, adherent jelly on right ovary. No comment on appendix
9	55	0	None	10 months	Free fluid	Loose jelly and widespread gelatinous nodules. Ruptured cyst of left ovary and smaller unruptured cyst of the right ovary. Mucocele of appendix with intact wall
10	51	1	Emergency appendicectomy 15 years before admission*	2 years	Tumour	Loose jelly. Ruptured cyst of right ovary and adherent jelly on left ovary and tubes
11	66	1	None	Not recorded	Free fluid	Loose jelly. Unruptured cyst of the right ovary. No comment on other ovary, uterus, tubes or appendix
12	59	0	None	1 year	Tumour	Neither free nor loculated jelly in the peritoneal cavity. A gelatinous nodule in anterior abdominal wall and another in caecal wall. Unruptured cyst of the left ovary and right ovary normal. No comment on appendix

* For details see text. † Microscopic examination revealed a cystadenocarcinoma.

primary operation 20 months prior to admission to the Women's Hospital. There was loose jelly, widespread gelatinous nodules in the peritoneal cavity and bilateral pseudomucinous cysts, the right being much larger than the left. The state of the appendix was not noted. Total hysterectomy, with removal of both appendages, was performed, with peritoneal toilet. The pathological report on the ovarian cysts confirmed that they were both cystadenomas and the biopsies taken of the nodules on the parietal peritoneum and the omentum contained mucinous material only. A second laparotomy 16 months later was restricted to the removal of a large quantity of jelly. Mrs. G. (Case 7), aged 45, had her original operation in the Women's Hospital in 1946. Loose jelly and a large loculus in the region of the spleen were noted, with gelatinous nodules on the pelvic peritoneum. A ruptured pseudomucinous cyst of the left ovary and an unruptured mucocele were present. Total hysterectomy, with removal of both appendages, appendicectomy and peritoneal toilet, were performed. The pseudomucinous cystadenoma and the mucocele were confirmed histologically. The biopsy of the peritoneal nodule contained jelly and portions of benign columnar epithelium similar to that lining the cyst.

A third patient (Case 4), aged 66, had a pseudomucinous cyst of the right ovary removed 2 years and 4 months prior to admission to the Women's Hospital at another constituent hospital of the United Birmingham group. The section has been reviewed and the diagnosis of a pseudomucinous cystadenoma confirmed.

The fourth patient (Case 10) had an emergency appendicectomy 15 years previously. She believed this was for acute appendicitis, but the diagnosis could not be confirmed.

The presenting symptom was enlargement of the abdomen and in just over half the cases this was associated with pressure symptoms. The duration of symptoms was less than 6 months in all but 3 cases.

Two signs were consistently elicited in the abdomen, either alone or in combination; a large cystic tumour and free fluid. On 2 occasions paracentesis abdominis was performed where the abdominal distension was obviously due to a large volume of free fluid and a small quantity of mucinous material was obtained. These were the only new cases in which a pre-operative diagnosis of pseudomyxoma peritonei was made. The observation that the positive clinical tests for free fluid in the abdomen were absent in 4 of the 11 cases in which it was found at laparotomy can be explained by the variations in the volume and viscosity of the pseudomyxomatous material. A fluid thrill is easily detected, but the dullness may not shift (Elliott, 1957; Brennan *et al.*, 1959).

At laparotomy the measured volume of loose jelly varied between 8 and 20 pints (4·5 and 11·3 litres). The peritoneum was often studded with adherent gelatinous nodules of varying size and attempts to remove them left raw areas. Commonly the omentum was extensively involved and on one occasion was described as a "rubbery plaque". Loculation of the jelly by parietal and visceral adhesions was common, particularly in those cases where a second or third laparotomy was necessary. A multilocular pseudomucinous ovarian cyst was associated in all cases and on 2 occasions they were bilateral. Eight of the cysts had spontaneously ruptured their capsules. A mucocele of the appendix was present in 4 cases and spontaneous rupture of the wall of the mucocele had occurred once. It is significant that 3 of the 5 patients in whom no comment on the appendix was made were advanced cases of the disease and full exploration of the abdomen was therefore probably impossible. In the last case on the table (12) a semi-solid nodule was encountered in the extra-peritoneal fat of the mid-line sub-umbilical incision. This was excised. The abdominal cavity was filled by a large pseudomucinous cyst of the left ovary; this was removed with the uterus and the other appendage because the tumour was assumed to be malignant. A second semi-solid nodule was found on the caecal wall and this was also excised. Neither loose jelly nor further implantations in the peritoneal cavity were found.

The ovarian cyst was removed, together with the other ovary, irrespective of its appearance, in all cases except one (Case 11). From the records of this case it would appear that she was a grave anaesthetic risk and, for that reason, surgical

TABLE II

Histological Findings

Case No.	Ovary: Type of Pseudomucinous Cyst	Extra-Ovarian Lesions: Jelly	Benign Epithelium	Malignant Cells	Inflammation	Appendix
1	Cystadenoma	+	−	−	−	Jelly implant
2	Cystadenoma*	+ +	− +	− −	− −	—
3	Cystadenoma	+	+	−	−	Mucocele
4	Cystadenocarcinoma	+	−	+	−	—
5	Cystadenoma	+ + + +	+ − − −	− − − −	− Chronic Chronic −	Mucocele
6	Cystadenocarcinoma	+	−	+	−	Jelly implant
7	Cystadenoma	+ +	+ −	− −	− −	Mucocele
8	(*a*) Cystadenoma (content infected)	+ +	+ +	− −	− Acute	—
9	Cystadenoma	+	+	−	−	Mucocele
10	Cystadenoma	+	−	−	Chronic	—
11	Cystadenoma (content infected)	+	+	−	Acute	—
12	Cystadenoma	−	−	−	Chronic	—

* Histology confirmed by letter.

interference was reduced to the minimum. Seven patients had a total hysterectomy and 6 an appendicectomy. As well as removing the involved organs the loose jelly was scooped out of the abdomen. On the whole, adherent visceral nodules were not removed because of the risk of perforation of the bowel, but biopsies were usually taken. Two patients (Cases 2 and 7) had a laparotomy only for the evacuation of large quantities of loose jelly. The abdomen was closed without drainage in every case. Following operation deep X-ray therapy was given to 4 patients.

PATHOLOGY

Sections from a total of 17 groups of operation specimens were re-examined microscopically (Table II). The characteristic epithelium of a pseudomucinous cystadenoma was found in 10 of the ovarian cysts (Fig. 1): a single layer of tall columnar cells with clear cytoplasm and basal nuclei. Excessive epithelial proliferative activity was not a feature. The specimen from Case 6 was an obvious malignant cyst on the original section and the diagnosis was re-confirmed (Fig. 2). One specimen (Case 4) was originally diagnosed as a cystadenoma, but

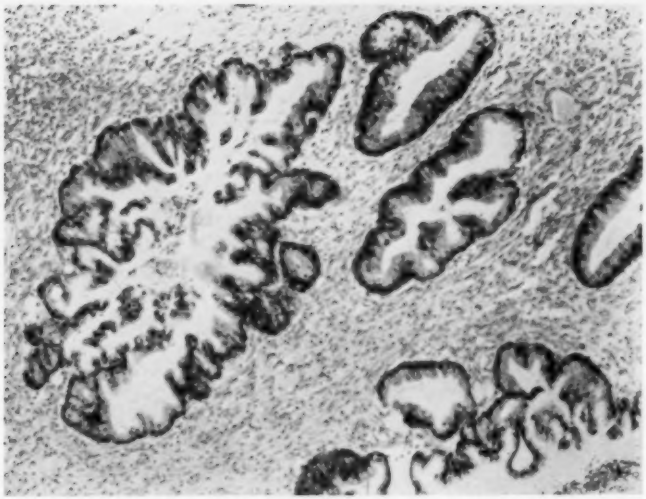

FIG. 1

Typical epithelial lining of ovarian cystadenoma (Case 1). Cysts lined by similar epithelium were found in Cases 3, 5, 7, 8, 9, 10, 11 and 12. ×70.

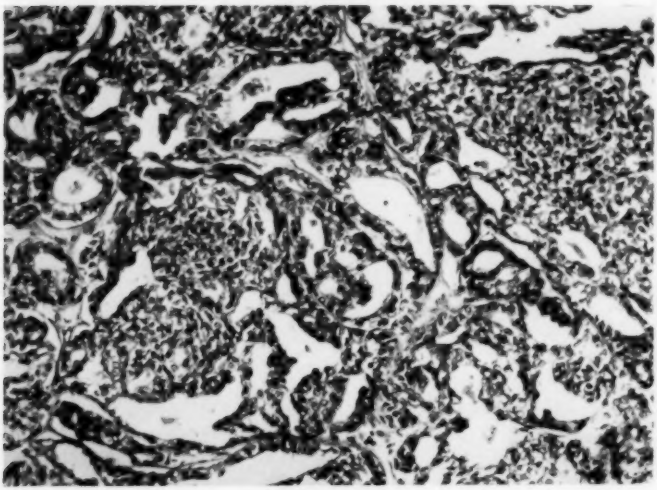

FIG. 2

Mucinous carcinoma of ovary (Case 6). ×110.

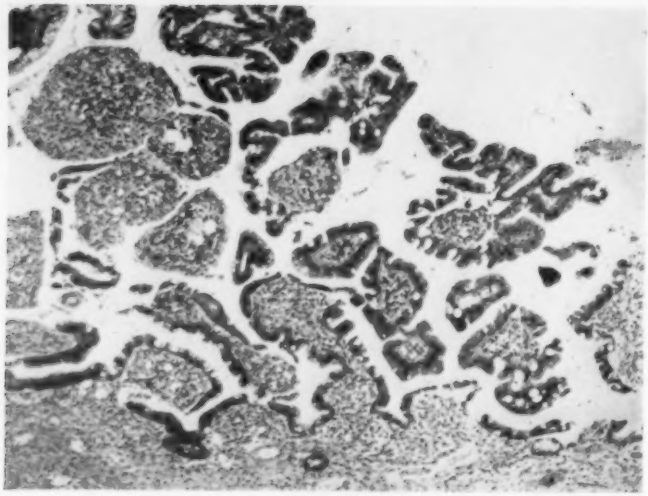

FIG. 3

Mucinous cyst of ovary showing epithelial proliferation with the formation of solid papillary in-growths (Case 4). ×70.

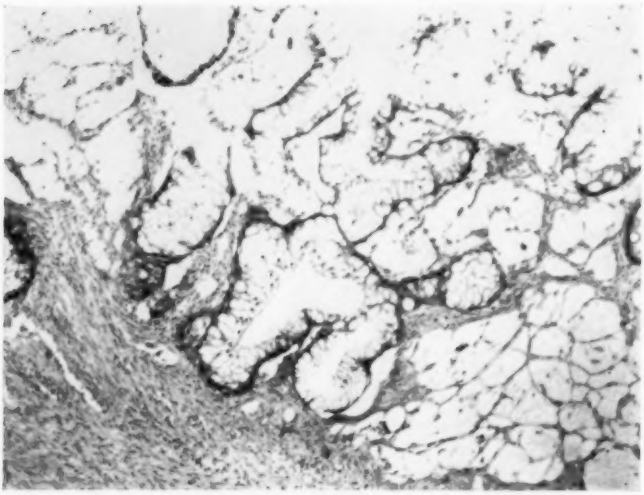

FIG. 4

Mucinous cystadenoma of ovary with melting down of epithelium and the formation of myxomatous tissue extending into the cyst wall. ×70.

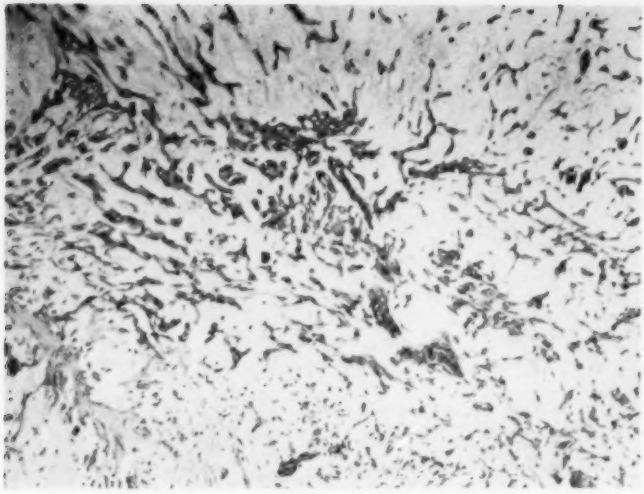

FIG. 5

Pseudomyxomatous jelly containing strands and cellular debris but no formed cellular elements. ×70.

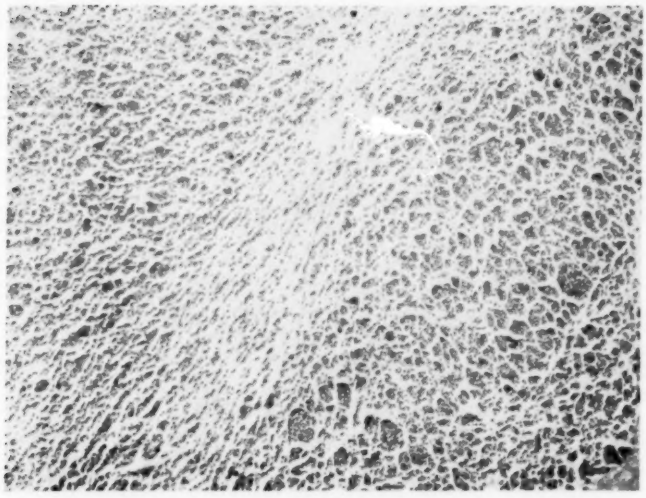

FIG. 6

Pseudomyxomatous jelly containing many leucocytes. ×70.

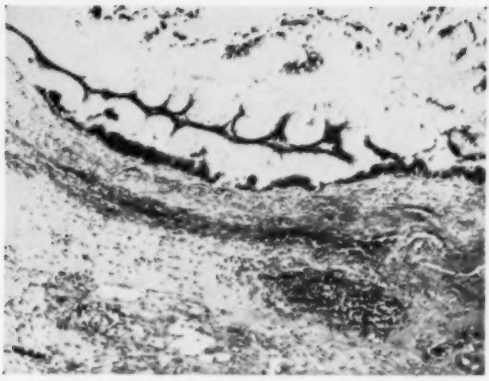

FIG. 7
Strips of mucinous epithelium attached to omentum. ×52.

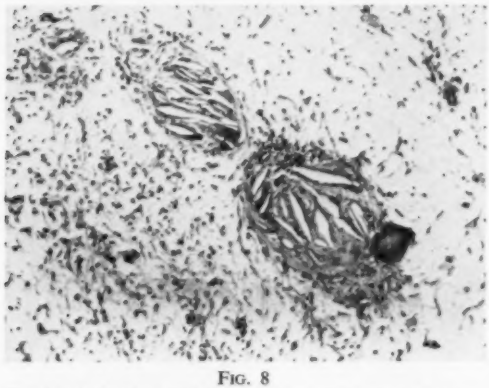

FIG. 8
Foreign body giant cells in pseudomyxomatous jelly. ×52.

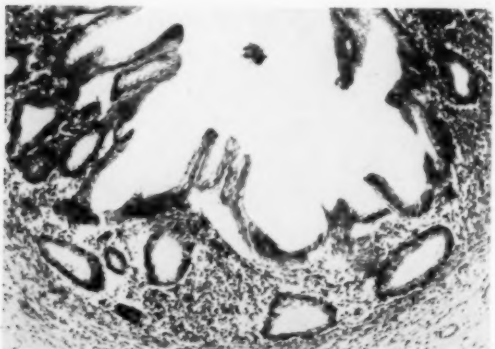

FIG. 9
Mucocele of appendix lined by mucus-secreting epithelium; the submucosa is thinned. ×82.

re-examination of the sections revealed such marked proliferative activity that the cyst was regraded as adenocarcinoma (Fig. 3). In half of the benign cysts we have observed a myxomatous appearance in the cyst wall: the columnar epithelium has disappeared and the mucinous secretion has infiltrated the fibrous tissue of the wall (Fig. 4). We mention this appearance as a possible precursor of spontaneous rupture of the cyst and pseudomyxoma peritonei.

Much of the loose jelly was acellular (Fig. 5). In several of our specimens it contained acute inflammatory cells (Fig. 6). Where the jelly is patchily adherent to the peritoneum or omentum, thus forming gelatinous nodules, or is loculated by adhesions, then strands of columnar secretory epithelium, identical to that which forms the distinctive lining of the pseudomucinous cystadenoma, can be found on section (Fig. 7). The affected tissues may also show a "foreign body" inflammatory reaction with lymphocytic infiltration and giant cell formation (Fig. 8). The microscopic appearances of the nodules removed from the anterior abdominal wall and the caecum (Case 12) were identical. They consisted of inspissated mucus surrounded by a chronic inflammatory reaction, but without an epithelial lining.

In those cases in which the appendix was replaced by a mucocele the lumen of the organ was distended by exudate and lined by tall columnar epithelium similar to that of a pseudomucinous cystadenoma of the ovary (Fig. 9).

TABLE III

Summary of the Pathological Findings

Ovary	No. of Cases	Extra-Ovarian Implants	
		Benign Epithelium	Malignant Epithelium
Cystadenoma ..	10	7	–
Cystadenocarcinoma	2	–	2

The pathological findings are summarized in Table III: of the 12 ovarian cysts 2 were malignant; of the 10 patients with benign cysts 7 had evidence of implantation of benign epithelium and, in the 4 patients in whom pseudomyxoma peritonei recurred, malignant degeneration of the explanted epithelium was not found.

RESULTS

There were no operative deaths following 17 operations in the Women's Hospital. Four patients apparently died from the natural course of the disease and this figure includes the 2 patients who had malignant cysts (Table IV). A fifth patient could not be traced and was included (assumed dead). The average length of life after diagnosis at operation was 1½ years and after the onset of symptoms 1¾ years. No patient died in the Women's Hospital and post-mortem examination has not been performed on

TABLE IV

Deaths

Case No.	Age	Pathology	Post-operative Survival	Certified Cause of Death
2	35	Benign	2 years	Inanition
4	66	Malignant	3 months	Pseudomyxoma peritonei
6	54	Malignant	2½ years	Carcinomatosis
8	66	Benign	1¼ years	Carcinoma cervix*
11	66	Benign	Untraced	

* For details see text.

TABLE V
Surviving Patients

Case	Age	Pathology	Interval Between Operation and Follow-up	Recurrence
1 ..	50	Benign	3½ years	Absent
3 ..	40	Benign	6 years	Absent
5 ..	44	Benign	6 years	Present
7 ..	57	Benign	14 years	Present
9 ..	55	Benign	6 months	Absent
10 ..	51	Benign	6 years	Absent
12 ..	59	Benign	4¼ years	Absent

any of the cases. A study of the certified cause of death in the 2 non-malignant cases did not throw any light on the terminal phases of the disease. A word of explanation is necessary to account for the diagnosis of carcinoma of the cervix (Case 8). The patient was re-admitted to the Women's Hospital 5 months after her primary operation with an implant of pseudomyxomatous tissue in the vaginal vault. This was considered to be inoperable and the patient died one year later in a geriatric unit where she was certified as a death from cervical cancer. Almost certainly this patient died from chronic sepsis and blood loss due to secondary infection of the vaginal growth.

The seven patients who are still alive were all examined in December, 1959 (Table V). Their average age is not so high as in the fatal cases. The period of follow-up varies between 14 years and 6 months, with 4 patients surviving 5 years. Two patients required further laparotomies for recurrences of pseudomyxoma peritonei. These were the only patients with clinical evidence of a recurrence at follow-up and we have briefly recorded their case histories:

Mrs. M. (Case 5), aged 44, was operated on for an abdominal tumour of moderate size in 1953. She had a benign pseudomucinous cyst of the left ovary, a ruptured mucocele of the appendix and pseudomyxoma peritonei. The cyst was removed, peritoneal toilet performed and the operation completed by total hysterectomy, removal of the other appendage and the appendix. In 1955 pseudomyxomatous material was found in the peritoneal sac of an inguinal hernia and she was given a course of deep X-ray therapy. One year later she had a second laparotomy for increasing abdominal discomfort and distension. The jelly was now loculated by dense adhesions and the largest loculus extended from the pelvis to the diaphragm; 12 pints (6·8 litres) of gelatinous fluid were removed and a biopsy taken from the wall of the loculus. Following operation radioactive gold was instilled. In 1958 she was re-admitted with recurrent symptoms and a third laparotomy was performed, removing a large quantity of jelly. When she was seen at the end of 1959, there was a cystic mass in the upper abdomen, extending downwards from the costal margin to within 3-finger breadths of the umbilicus. No signs of malignant degeneration of the epithelium were found in the biopsy material.

Mrs. G. (Case 7), aged 45, was operated on for a vast abdominal tumour in 1946 and the findings and the procedure have already been recounted. The patient remained well until the autumn of 1958, when she was re-admitted complaining of enlargement of the abdomen. Twenty pints (11·3 litres) of jelly were scooped out of a loculus occupying the left side of the abdominal cavity. The small intestine was sealed off in the right upper quadrant and a second loculus was present in the pelvis. This was also evacuated. Seven weeks after operation there was a spontaneous discharge of "slime" and pus from the upper end of the laparotomy scar. This was associated with a swinging temperature and it was at first feared that the patient had developed a faecal fistula, due to spontaneous perforation of the bowel by pseudomyxomatous infiltration. The temperature settled, but infected mucinous material continued to discharge from the sinus. When she was seen at follow-up in December, 1959, she was well and had gained a stone in weight since laparotomy the previous year. The abdomen was not distended and the sinus required dressing only twice daily. The pelvic mass was still palpable bimanually. Malignant epithelium was not found in the biopsy material from this patient.

DISCUSSION

Aetiology

The general appearance of pseudomyxoma peritonei with infiltrated omentum, widespread implants and adhesions suggests peritoneal carcinomatosis. The site of entry of the mucus-secreting tumour cells into the abdominal cavity appears to be, in the vast majority of females, an ovarian cyst. In the first volume of his *Diseases of the Ovaries* Spencer Wells (1865) describes 2 cases which are typical of pseudomyxoma and he believed that the lesions were the result of a colloid carcinomatosis of the peritoneum. Almost a century later Malpas

has proposed that most, and perhaps all, cases of pseudomyxoma peritonei associated with ovarian tumours are malignant in the long run.

A study of Cariker and Dockerty's comprehensive paper (1954) on the biological behaviour of mucinous tumours of the ovary supports this proposition. They record pseudomyxoma peritonei as a complication of 44 tumours, all of which were cystadenocarcinomas. Our experience in the Women's Hospital has been quite the reverse, with pseudomyxoma presenting on 2 occasions only as a complication of pseudomucinous cystadenocarcinoma, an incidence of malignancy of only 17 per cent. Wilson (1912) did not find a malignant case of pseudomyxoma peritonei in a personal series of 331 ovarian tumours and one gathers from von Nagy's paper (1933) (although he does not specifically detail the pathology of every case) that he did not have a malignant cyst among his series of 10 cases.

There is great difficulty in attempting to evaluate the quoted incidence of malignancy in different series of ovarian cysts because of lack of uniformity in the interpretation of the criteria of malignancy. In the Mayo Clinic the incidence of malignancy in pseudomucinous cysts is 39 per cent, whereas in Birmingham it is about half that figure at 19·2 per cent. The latter figure corresponds to von Nagy's 17·2 per cent. A possible explanation of this variation is contained in Cariker and Dockerty's paper. They state that:

> "The persistent search for malignant *cytological* changes in the cysts in our series may account, we feel, for the higher incidence of malignant lesions. Of the malignant lesions classified as Grade 1, more than half showed malignant growth in only part of the cyst wall, or in only a small region."

In fact they placed 100, out of a total of 138, cystadenocarcinomas in Broder's Grade 1 and 32 of the pseudomyxoma cases occurred in this group.

The difficulty is also apparent when the histology of pseudomyxoma peritonei is studied and is illustrated by the fact that Masson and Hamrick also analyzed the Mayo Clinic series in 1930 and found only a 43 per cent incidence of malignancy in the 30 cases recorded up to that time. Willis (1952) sums up the histological problem when he states that no sharp distinction can be made between pseudomyxoma peritonei secondary to a structurally benign ovarian cystoma and gelatinous carcinoma of the peritoneum secondary to a frankly malignant ovarian tumour.

Therefore we turned to an examination of the survival rates as a further aid towards a distinction between benign and malignant. A 5-year survival was accepted as an indication of the benign nature of the disease and in fact all our fatalities occurred within 3 years. When the Mayo Clinic patients were followed up, Cariker and Dockerty (1954) found 6 had survived 5 years after operation (2 could not be traced). Of our 12 patients 4 survived 5 years (1 could not be traced) and of Wilson's cases 2 patients, out of the 5 who survived operation, were alive and well after 5 years. Approximately 1 patient in 7 survived 5 years in the American series and 1 in 3 in Birmingham and these figures, although small, appear to confirm that the low incidence of malignancy in the British series is not entirely due to differences in pathological interpretation.

From our study by histology and follow-up it may be concluded that pseudomyxoma peritonei is neither invariably associated with malignant disease of the ovary, nor is it always fatal.

Before one can accept a causal relationship between the benign cyst and pseudomyxoma peritonei 3 problems must be faced.

Firstly pseudomucinous cystadenomas are relatively common, yet the complication of pseudomyxoma peritonei is rare. It is generally accepted that the main source of the jelly is the direct spill of the contents of a ruptured loculus into the peritoneal cavity and continuing extravasation from the mucus-secreting epithelial lining of the cyst. To re-state the problem one might ask—why do some cysts rupture and others, of equal or greater size, do not?

Trauma to the abdominal contents as a result of external violence can be excluded as a factor, since rupture is invariably silent. Malpas points out that silent rupture is characteristic of infiltration of the malignant cyst wall by its invasive lining epithelium. Wilson believed that the jelly-like consistency of the contents of the

loculus oozing slowly into the peritoneal cavity explained the lack of dramatic signs which usually accompany perforation of a hollow organ. He points out that progressive accumulation of jelly within the cyst results in thinning of its wall and ultimately pressure atrophy of areas of its capsule. It is an everyday experience, however, that many cysts reach an enormous size without dehiscence of their walls. Is it possible that there is a particular change within the cyst wall which favours rupture? We have already described a myxomatous appearance in the wall of many cysts, but this change was not present in all cases. It is doubtful, even when present, if it is a specific factor in the aetiology of pseudomyxoma peritonei from a benign cyst.

In contrast to insidious rupture accidental spilling of the gelatinous content of a benign cyst, during removal or evacuation before removal, rarely leads to pseudomyxoma peritonei. Cariker and Dockerty (1954) report that spilling occurred on 63 occasions in the course of 217 laparotomies for benign mucinous tumours, without the development of pseudomyxoma. They also found in their series that accidental rupture of a malignant cyst even, did not affect the prognosis adversely. The explanation is not clear and the possibilities are discussed later.

Secondly, in an appreciable number of patients pseudomucinous material will re-accumulate again in the abdominal cavity after all ovarian tissue has been removed. Extra-ovarian lesions must be responsible for the continued production of jelly and the pathogenesis of these lesions is, at first sight, difficult to account for except on the basis of a malignant disease.

When we re-examined sections of the extra-ovarian peritoneal lesions removed at the primary operation or at a subsequent laparotomy there was no evidence of malignant degeneration. When epithelium was seen, it conformed to the distinctive type which lines the pseudomucinous cystadenoma.

Two theories are in current use to account for the presence of these portions of columnar epithelium which patchily line the plaques of jelly which adhere to the peritoneal surfaces and the irregular cystic spaces formed by adhesions in the abdominal cavity. The generally accepted theory (Novak, 1952; Willis, 1952) postulates that living strands of epithelium are cast off from the lining of the cyst and escape with leaking jelly to become attached anywhere in the peritoneal cavity. There they continue to secrete mucus and to proliferate.

A second theory is still widely held (Shaw, 1952) and is based on the original theory of Werth (1884). The extravasated jelly exerts an irritant action on the peritoneum, which results in a foreign body type of inflammatory response producing adhesion of the jelly and of the affected peritoneal surfaces. As a sequel the mesothelium of the peritoneum is converted, in part, into tall columnar epithelium which is histologically similar to that lining a pseudomucinous cystadenoma. These cells secrete mucinous material into the peritoneal cavity. Thus the emphasis is placed in this theory on the mucinous content of the cyst as the agent responsible for the intra-peritoneal lesions, rather than the explanted cells.

It seems probable that both the fluid and the cells play a part in the production of the extra-ovarian lesions. The recurrence of pseudomyxoma in some patients and not in others may be explained by the balance struck, in the individual patient, between the proliferative activity of the epithelial implants and the efficiency of the inflammatory reaction of the peritoneum to ultimately enmesh the epithelium in fibrosis. Masson and Hamrick suggest that resumption of mucin secretion after a long interval may be due to a fresh intra-peritoneal spill of gelatinous material and cells from a loculus which had, prior to rupture, remained encapsulated since the primary operation.

The interaction of the chronic inflammatory activity produced in the peritoneum and the shed epithelial strands may also explain the rarity of pseudomyxoma as a sequel of aceidental spilling during removal. It is possible that the irritant jelly requires to be in contact with the peritoneum long enough to induce a reaction in the serosa, which will allow epithelial implantation to take place.

The third problem centres around the short period of survival of a number of patients and some gynaecological textbooks give the impression that they are the majority.

Unfortunately we have not had the advantage of examining post-mortem the fatal non-malignant cases. However, from a study of the literature it is apparent that the causes of death fall into one or other of 3 categories:

(1) A number die from sepsis. Traumatic or spontaneous perforation of the bowel is a not uncommon complication and the patient dies either soon after operation or at a later date from toxaemia due to a localized intra-peritoneal or retro-peritoneal abscess. Wilson describes a retro-peritoneal abscess causing death 2 years after operation.

(2) A number die from mechanical interference with alimentary tract function. Intestinal obstruction due to kinking by adhesions is relatively common. Masson and Hamrick report a case of obstructive dilatation of the stomach due to a cystic mass at the pylorus and another case of deep jaundice due to pressure on the common bile duct.

(3) A number die from pulmonary embolism. Intra-abdominal compression of the major veins with stasis predisposes to deep venous thrombosis.

Pseudomyxoma Peritonei of Appendicular Origin

Pseudomyxoma peritonei of appendicular origin is a rare disease. Elliott (1957) reported that only 2 cases were seen in the United Oxford Hospitals between 1938 and 1956. During the same period 30 mucoceles of the appendix were diagnosed in the course of approximately 13,000 appendicectomies—an incidence of 0·2 per cent. In the ten-year period 1950–59 only 1 case has been traced in the United Birmingham Hospitals. This was a married woman aged 22, who was admitted to the Women's Hospital in May, 1955, complaining of one child sterility. A salpingogram had shown limited tubal spill, probably due to pelvic adhesions and laparotomy was undertaken entirely on these findings. The pelvis was full of gelatinous fluid, there were numerous adhesions between the ovaries and the tubes and the ovaries were otherwise normal. Peritoneal implantation had not occurred. The appendix was replaced by a mucocele which had ruptured spontaneously. Appendicectomy was performed followed by salpingolysis. Histological examination of the appendix confirmed the presence of a mucocele. No epithelium was seen in the specimen of jelly sectioned. Since operation she has conceived 4 times, but on each occasion has failed to carry the pregnancy beyond the 3rd month. She was last seen at Out-Patients in July, 1958, and at that time there was no evidence of a recurrence of pseudomyxoma peritonei. Her family doctor reported in December, 1959, that she was alive and well.

The appendicular lesion is commonly a perforated mucocele, but a number follow rupture of an adenocarcinoma (Masson and Hamrick, 1930). The pathogenesis of the benign case is still unsettled and the controversy, as in the case of the benign ovarian cyst, centres on the origin of the columnar epithelium. Experimentally, pseudomyxoma peritonei closely resembling that in human beings can be produced in young rabbits (Cheng, 1949). Transplantation of appendicular cells does not occur and the conclusion was that the general appearance of the abdominal cavity was entirely due to the peritoneal foreign body reaction. This laboratory work supports the theory of serosal metaplasia. It is not always possible, however, to transfer an argument based on data obtained in one species to a different one and Willis believes that the difference between ovarian and appendicular pseudomyxoma is one of degree only: an ovarian cyst yielding much more mucus and epithelium than a mucocele whose epithelium possesses the power of mucus-formation and proliferation only to a physiological degree. Whatever the reason there is little doubt that the appendicular form of the disease has a better prognosis than the ovarian (Masson and Hamrick, 1930).

It is interesting to note that 4 of our 12 cases had a mucocele of the appendix as well as a pseudomucinous cyst; this combination has rarely been observed in the clinical practice of the hospital in the absence of pseudomyxoma peritonei. In the literature the association is well known but the sequence of events is not clear. The appendicular disease may be primary where the mucocele is the result of a colloid adenocarcinoma, but this is not the common association. The possibility of non-neoplastic

intestinal epithelium implanting on the ovary and producing a typical pseudomucinous cyst is unlikely. Willis believes that the ovarian disease is primary and the appendicular lesion is secondary, suggesting that the appendix is infiltrated from without by implants of mucus-secreting epithelium which ultimately replace its wall. In our material we have seen patches of epithelium and jelly on the peritoneal coat of the appendix, but we have not found any intermediate stages between this lesion and the typical mucocele to support this hypothesis.

The association is too frequent to be coincidental. Fisher (1954) has investigated the chemical nature of the fluid content and the cellular secretion of pseudomucinous cysts. He has demonstrated that these substances are chemically identical with mucin—both are muco-polysaccharides and not, as was originally thought, glycoproteins. The similarity in the chemistry of the content of the cyst and the mucocele and the similarity in cellular lining indicate a very close kinship, but the significance of the association is so far unexplained.

Treatment

Treatment is based on surgical measures and laparotomy is necessary to establish the diagnosis, remove the primary cyst and relieve pressure symptoms by scooping out as much of the jelly as possible. Implants are common on the peritoneal surfaces of all the pelvic organs and, since the majority of patients are past the menopause, removal of the uterus and the other ovary is logical. The frequent association with a mucocele of the appendix makes appendicectomy an essential additional procedure.

The loose jelly is easily scooped out of the abdominal cavity, but a greater or lesser quantity must necessarily be left behind, where it adheres firmly to the parietal and visceral peritoneum. From our knowledge of the pathogenesis of pseudomyxoma it would seem logical to reduce the extent of the peritoneal implants to a minimum and Malpas (1959) reports extensive stripping and dissection of gelatinous masses from the intestines and the parietal peritoneum. When the omentum is extensively involved it should be removed.

In our experience relief of pressure symptoms is the commonest indication for further surgical treatment and repeated laparotomies may be necessary to remove a vast quantity of jelly. The ideal, as suggested by Malpas, would be repeated tapping of the abdomen, but in our hands this minor procedure has not been of any value. Several authors (Strauss and Strauss, 1952; Brennan *et al.*, 1959) have suggested the addition of enzymes to the mucus to render it more fluid. Laparotomy may also be required to relieve a mechanical intestinal obstruction due to adhesions.

Worthwhile information on the value of radiotherapy is difficult to obtain. In the United States it is generally agreed that deep X-ray therapy should be given post-operatively. The experience of the Mayo Clinic, reported by Cariker and Dockerty (1954), was that it would not cure pseudomyxoma, but was of help in delaying spread. Malpas (1959) states that pseudomyxoma peritonei is radio-resistant. Our experience of a small number of cases was disappointing. However, one of our patients (Case 6) with pseudomyxoma secondary to a mucinous ovarian carcinoma lived in comfort for 3 years after operation, while recurrences in the pelvis and the upper abdomen were kept in check by irradiation. We feel, in principle, that the efficiency of radiotherapy is open to doubt in any non-malignant condition, as are the majority of cases of pseudomyxoma peritonei, but where the disease is a form of peritoneal carcinomatosis, then it is logical to prescribe it. The variation in the incidence of malignancy in pseudomyxoma previously noted may explain the diverse opinions of the value of radiotherapy.

Prognosis

All our patients survived operation. In many recorded cases this has not always been so and infection appears to have been the chief cause of operative death. In 1930 Masson and Hamrick reported an operative mortality of 12·8 per cent in the Mayo Clinic: 3 patients died of peritonitis and 2 from pulmonary embolism.

According to Willis (1952) the ultimate prognosis depends on the growth capacities of

TABLE VI

Possible Factors Influencing the Prognosis

Case No.	Age	Extent of Disease	Ovarian Cyst	Implants	Post-operative Radiotherapy	Result
1	50	Restricted	Benign	Absent	Not given	Alive
2	35	Widespread	Benign	Present	Given	Dead
3	40	Restricted	Benign	Present	Not given	Alive
4	66	Widespread	Malignant	Present	Not given	Dead
5	44	Widespread	Benign	Present	Given	Recurrent
6	54	Widespread	Malignant	Present	Given	Dead
7	57	Widespread	Benign	Present	Not given	Recurrent
8	66	Restricted	Benign	Present	Not given	Dead
9	55	Widespread	Benign	Present	Given	Alive*
10	51	Restricted	Benign	Absent	Not given	Alive
11	66	Restricted	Benign	Present	Not given	Untraced
12	59	Restricted	Benign	Absent	Not given	Alive

* Follow-up 6 months only.

the responsible epithelium and he elaborates by stating that "it is good in appendical cases, doubtful in 'benign' ovarian cases and hopeless in carcinomatous cases". During the preparation of this review we hoped to find a factor or factors which could be used to formulate a guide to the prognosis for the individual patient. We had already noted Schumann's (1908) suggestion that the pseudomyxoma complicating benign cysts of the ovary might, on some occasions, be chiefly a foreign body peritonitis (by inference, a self-limiting disease when the irritant was removed) and, on other occasions, a metastatic phenomenon. This may over-simplify the problem, but our investigation shows that it is not without a factual basis (Table VI). Extensive involvement of the peritoneal cavity and histological demonstration of explanted cells is associated with a recurrence of the disease and, in some patients, a fatal outcome.

SUMMARY

A clinical and pathological study has been made of 13 cases of pseudomyxoma peritonei in women. Twelve cases were associated with pseudomucinous tumours of the ovary, 10 of which were benign and 2 were malignant. One case followed rupture of a mucocele of the appendix.

Pseudomyxoma peritonei is a rare complication of a pseudomucinous ovarian tumour and occurred in 3·5 per cent of 337 cases. The source of the jelly is partly the leaking cyst secretion and partly the epithelial implants scattered over the peritoneum. Other characteristic features of the disease are the result of attempts by the peritoneum to localize the jelly with the formation of dense adhesions and encapsulated collections.

Pseudomyxoma peritonei of appendicular origin is an even rarer disease. Yet the association of a pseudomucinous cyst and a mucocele

of the appendix is not uncommon in pseudomyxoma peritonei in females and was found in 4 of the present series of cases. The significance of this association is unexplained.

The treatment is surgical and the value of radiotherapy is not proven. Of the 12 ovarian cases studied, 4 died and 1 was not traced. In the patients who died, the ovarian lesion was malignant in 2 and benign in 2. In the 7 patients who have survived, 2 are alive with a recurrence of the disease, one 14 years and one 6 years after diagnosis. Five patients have survived without evidence of recurrence for periods varying from 6 months to 6 years. The case following rupture of an appendicular mucocele is alive and free of recurrence three and a half years after operation.

The prognosis of pseudomyxoma peritonei complicating a benign mucinous cyst of the ovary is always doubtful.

Acknowledgments

I wish to express my sincere thanks to Dr. Claud Taylor, the Director of Pathology at the Birmingham and Midland Hospitals for Women, for the review of the pathological material and helpful suggestions and criticism of the paper during the period of preparation. I am indebted also to the Consultant Staff of the Birmingham and Midland Hospitals for Women for allowing me to study the case records and to follow up the patients admitted under their care; to Dr. Hans Kohler for translation of the German literature; and to Mr. W. R. Lea for the photomicrographs.

Addendum

Since this article was submitted for publication, Case 9 in Table VI has been re-admitted to the Women's Hospital (18 months after the original operation) with a recurrence of pseudomyxoma peritonei. At laparotomy the recurrence was found to be widespread in the peritoneal cavity and 3½ pints (2 litres) of loose jelly were removed. A mass was excised from the omentum for microscopical examination which showed typical pseudomyxoma peritonei with strips of benign columnar epithelium.

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TWO CONTRASTING CASES OF CHORIOADENOMA DESTRUENS

BY

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HYDATIDIFORM mole is encountered once in every 300 pregnancies admitted into the Kandang Kerbau Hospital, Singapore. This compares with 1 in 530 in Hong Kong (King, 1956) and is about 7 to 10 times the reported frequency in Western communities. The occurrence of invasive changes or chorioadenoma destruens is said to be 7 per cent (Hunt *et al.*, 1953) and 8 per cent (Coppleson, 1958).

The name chorioadenoma destruens was given by Ewing in 1910 to a type of hydatidiform mole which showed marked local invasion and even perforation of the uterus. Since it is generally agreed that metastases seldom if ever occur (Kuperstein and Mackles, 1954; Novak and Seah, 1954; Coppleson, 1958; King, 1956; Logan and Motyloff, 1958; Hertig and Sheldon, 1947), differentiation from choriocarcinoma is of primary importance.

Hertig and Sheldon (1947) state that the malignancy of a lesion can be determined by the degree to which the cell morphology resembles that of the trophoblast of the ovum during its first week after implantation, the cells of which bear a close resemblance to those of choriocarcinoma. However, the majority of authorities disagree and among others Novak (1952), Hunt, Dockerty and Randall (1953) were unable to correlate cell morphology with malignancy.

To complicate matters further, Schmorl (1904) found syncytium in the pulmonary capillaries of 80 per cent of his autopsies on women dying during pregnancy and Marcuse (1954) states that benign trophoblastic emboli in sufficient quantity can cause death during normal pregnancy.

If numerous well-formed villi are present, the condition is unlikely to be one of choriocarcinoma (Novak, 1952; Johnston, 1955; Coppleson, 1958).

Hobson (1959) states that chorioadenoma and choriocarcinoma cannot be distinguished by the amount of chorionic gonadotrophin excreted before hysterectomy, although after hysterectomy the titre falls rapidly in the case of the former but not in the latter.

The treatment advised by most authors is hysterectomy with, possibly, conservation of one ovary in young women, though Hertig and Sheldon (1947) are of the opinion that the uterus should not be sacrificed. According to Kuperstein and Mackles (1954) death occurs from perforation, sepsis, or haemorrhage but not as a result of metastases.

The two cases which will be described demonstrate the difficulty in treatment in patients where chorioadenoma destruens appeared to be the correct diagnosis from clinical, histological and gonadotrophin assessment.

Case 1

The patient, H.E.L., was a 17-year-old, unmarried Chinese girl. She was referred to one of us (J.W.F.L.) on the 24th August, 1956 with a complaint of nausea and vomiting for 3 weeks and lower abdominal colic for a week. Her last menstrual period began on the 15th August, was excessive in amount and intermittent

spotting had been present since. There had not been any period of amenorrhoea. Her normal cycle lasted seven days every twenty-eight days. She suffered from diurnal frequency of micturition, had had a bout of fever two days before and had noticed an abdominal mass for three days.

Abdominal examination revealed a uterine enlargement corresponding to 16-weeks gestation. There were no signs of a foetus being present. On vaginal examination the introitus admitted two fingers; the uterine enlargement was confirmed and the cervical os was closed.

The patient was admitted into hospital. She was not anaemic and her blood pressure was normal. A male toad test the following day was positive. During the next three days, the uterus increased in size to reach the level of the umbilicus. There was a sudden onset of severe abdominal pain. A diagnosis of hydatidiform mole was made and the uterus was evacuated of a molar pregnancy by the vaginal route on the same day. Histological examination showed molar tissue with hyperchromatic Langhans' cells.

When the patient was seen one month later, she did not have any complaint except for a slight pink vaginal discharge. Pelvic examination revealed a patulous os, a slightly bulky uterus and cystic ovaries, each the size of a grapefruit. A quantitative toad test on the serum was positive in 1:2 dilution.

On the 6th October curettage was performed. Two large ovarian cysts were still present. The cavity of the uterus was 5¼ inches long and a few fragments of material were removed by the curette. The histological report read as follows: "Blood, villi and necrotic tissue seen. Large groups of syncytial and Langhans' cells with marked mitoses also seen. Villi cellular with similar cells. Diagnosis: mole with malignancy (chorionepithelioma)" (Fig. 1).

A serum toad test repeated at this time was positive in 1:40 dilution. A chest X-ray did not show any abnormality.

On the 24th October the toad test was negative but the ovarian cysts appeared larger and were tender. She was admitted. On the 25th October a laparotomy was performed. Bilateral ovarian cysts were resected and the ovaries reconstructed. The right uterine cornu was found to have been replaced by a haemorrhagic mass, two centimetres in diameter, with intact peritoneum covering it. No local secondary deposits were discovered. The right cornu was excised and the proximal unaffected part of the right tube implanted into the uterus. Histological examination showed an invasive mole with well-formed villi and sheets of very active trophoblast (Fig. 2).

The patient made an uneventful recovery and subsequent toad tests were negative.

The patient married one year later and on the 18th November, 1958 was referred because she had failed to conceive. Her cycle was regular, two days every 21 to 25 days. A dilatation and insufflation was done on the 22nd November. Gas passed at 180 millimetres pressure, apparently through both tubes.

One further menses occurred on the 26th December and on the 25th February, 1959 a toad test on her urine was positive. Her pregnancy was normal except for a mild hypochromic anaemia which responded to oral iron. The Kahn test was negative and the blood group "O", Rhesus positive. She was admitted in labour on the 2nd September, 1959 (35½-weeks gestation) and was delivered easily soon after admission of a female baby weighing 3 pounds 6 ounces. The placenta was expelled normally after ten minutes with minimal blood loss.

The infant was treated in the premature nursery and was discharged well after one month. The mother failed to lactate.

Comments

The problem in this case was to decide whether choriocarcinoma was present or not. The original histological diagnosis did not seem justified in view of the presence of many well-formed villi, although great trophoblastic activity was evident.

The decision to retain the uterus, contrary to accepted practice, was influenced by the patient's age and the knowledge that her fiancé would only marry her if her childbearing capacity was retained. The re-implantation of the right tube into the uterus was, perhaps, unwise as it would further weaken the scar and the left tube appeared to be normal. A decision was made to deliver the patient by abdominal section at 38-weeks gestation but this was forestalled by premature labour and delivery soon after she reached the hospital.

This appears to be a typical case of a locally invasive mole and the conservation of the uterus is justified by the result.

Case 2

A Chinese primigravida, W.J.M., aged 19, was first seen by one of us (S.H.T.) at the Gynaecological Outpatient Department of this hospital on 14th October, 1959 with symptoms of severe nausea and vomiting for the past month. She had been married only 3 months. Her last menstrual period began on 13th July, 1959. Her periods were regular, 3 days every 30 days. The period of amenorrhoea was 13 weeks. There was no history of vaginal bleeding.

On examination, the patient was very anaemic. The temperature was 99·8° Fahrenheit, blood pressure 134/80 mm. mercury and the pulse rate 116 per minute. The uterine size corresponded to a 16-weeks pregnancy. A diagnosis of hyperemesis and anaemia of pregnancy was made and the patient admitted into hospital.

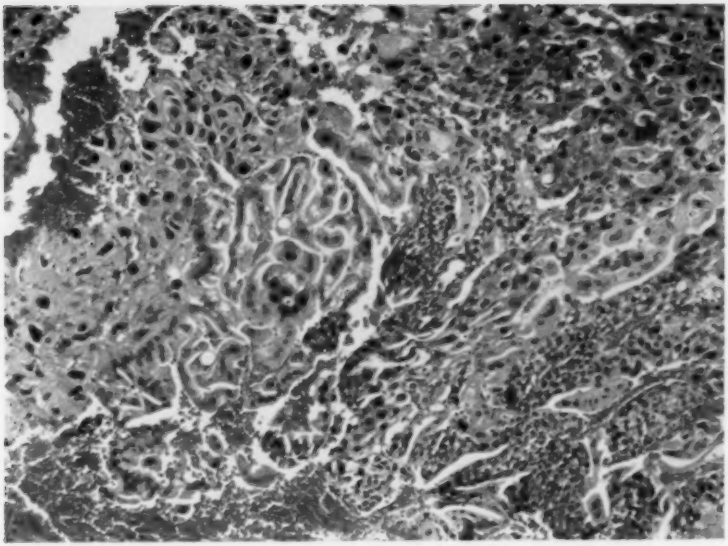

FIG. 1

Case 1. A section of the curettings showing an area without villi and with hyperplasia of Langhans' cells and syncytium, very suggestive of choriocarcinoma. H. & E. ×100.

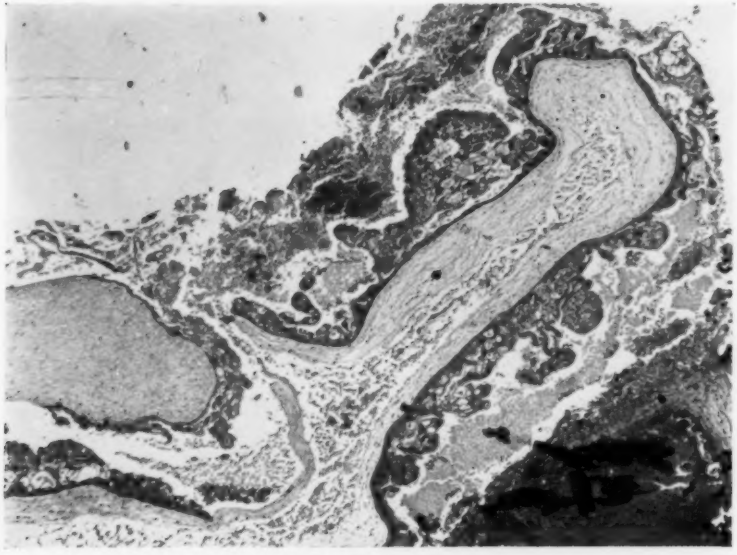

FIG. 2

Case 1. A section of the wall of the uterus showing necrosis of uterine muscle and well-formed villi. H. & E. ×40.

FIG. 3

Perforating mole: appearance at operation (Case 2). The uterus is perforated anteriorly. Both ovaries are enlarged by multiple cysts.

FIG. 4

Uterus: perforating mole (Case 2). Chorionic villi are seen invading the whole thickness of the uterine muscle and some appear on the serous surface. H. & E. ×5.

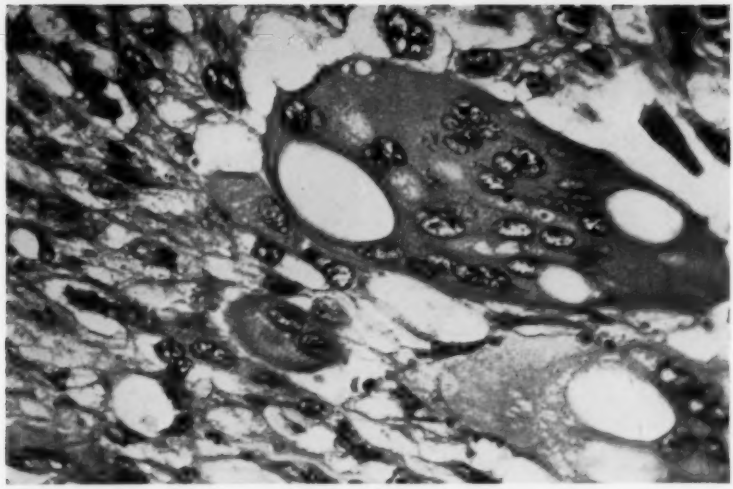

FIG. 5

High power section from an area of trophoblastic hyperplasia showing Langhans' cells and syncytial tissue with vacuolation. H. & E. ×400.

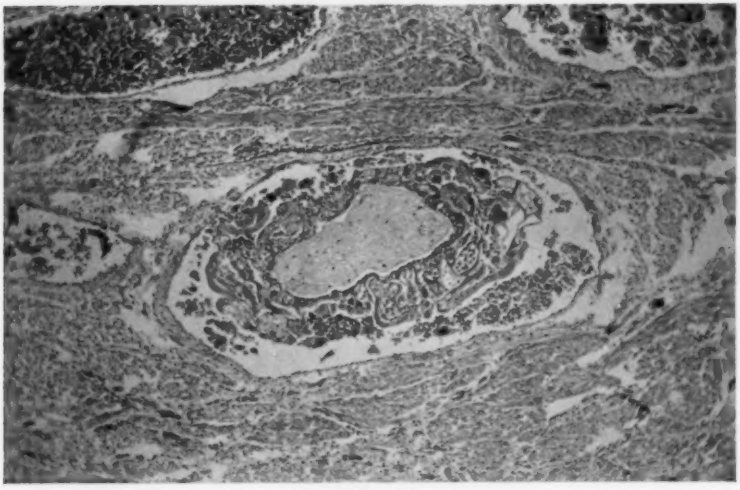

FIG. 6

Uterus, post-mortem section (Case 2). The myometrium is extensively infiltrated by groups of trophoblastic cells which are found especially within the uterine veins. One chorionic villus is clearly shown. H. & E. ×63.

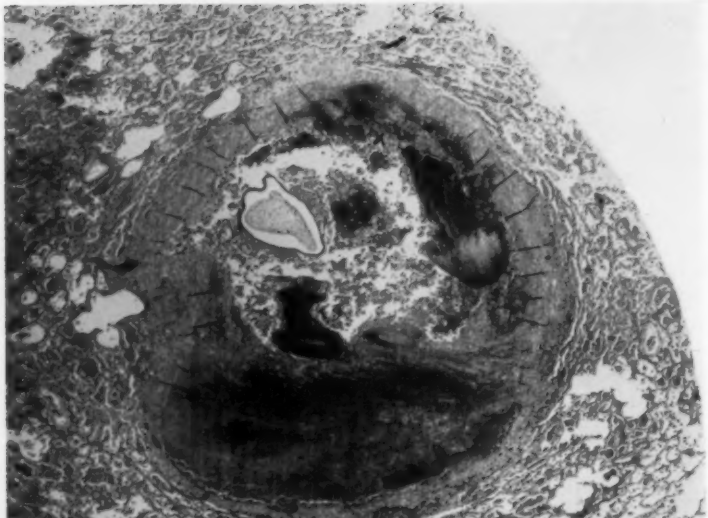

FIG. 7

Lung (Case 2). A circular area of haemorrhage with one chorionic villus. H. & E. ×20.

First Admission. Investigations showed a typical iron deficiency anaemia with a haemoglobin of 31 per cent. Injections of Imferon, 4 ml., were given on alternate days and tablets of meclozine hydrochloride 25 mg. twice daily. Her symptoms were relieved to a large extent and she was able to retain a high protein diet. Four pints of packed cells were given. The patient was discharged on 23rd October.

Second Admission. Two days later the patient was re-admitted at 1.30 a.m. complaining of sudden severe pain in the lower abdomen for 4 hours. The pain spread rapidly upwards to the lumbar regions on either side. There was no vaginal bleeding. On examination it was evident that there was internal haemorrhage. The patient was pale and shocked, the blood pressure was 100/70 mm. mercury and the pulse rate 108 per minute. There was marked tenderness and guarding over the whole abdomen. Shifting dullness was present.

Preparations were made for immediate laparotomy. With the patient under anaesthetic, a bimanual examination was performed. The uterine size was consistent with a 16-weeks pregnancy. The enlargement was symmetrical and of a tense cystic or doughy consistency. Ballottement could not be elicited. Two mobile soft cystic masses, each the size of a fist were felt in the lateral fornices. On these findings a diagnosis of perforating hydatidiform mole was made.

At operation the diagnosis was confirmed. The enlarged uterus was eroded on its anterior aspect at the upper portion of the lower third (Fig. 3). There was an irregular perforation about the area of a sixpence, with molar tissue exuding from the uterine cavity on to the serosal surface. A steady ooze of blood flowed from the disrupted myometrial edges. There were more than two pints of free blood and clots in the peritoneal cavity. Both ovaries were enlarged by multiple thin-walled cysts containing clear serous fluid.

The perforation was excised by means of a wide elliptical incision through which the uterus was evacuated of its molar contents. The uterine cavity was thoroughly curetted, the incision sutured and the abdomen closed. Two pints of blood were transfused. The convalescence was uneventful and the patient returned home on the 7th day with a haemoglobin of 55 per cent. At the follow-up clinic on 9th November, 1959 the patient was looking very well. The urine toad test was strongly positive.

Third Admission. On 1st December, 1959, while out for a walk in the park at 7 p.m., the patient was suddenly seized with intense headache, giddiness, vomiting and blurred vision. She threw a fit, lapsed into coma and was immediately brought to hospital. She died soon afterwards without regaining consciousness. An autopsy was performed the next day.

Pathological Report

The section of uterine muscle excised at laparotomy showed invasion of the whole thickness of the uterine wall by chorionic villi and masses of trophoblastic cells (Fig. 4). The villi are present in the depths of the uterine muscle and appear on the serous surface through a perforation. There is marked trophoblastic hyperplasia (Fig. 5) and atypical Langhans' cells and syncytial masses are present in association with the villi—appearances characteristic of a malignant hydatidiform mole.

Autopsy Findings

The uterus was twice normal size with a recently healed midline scar on its anterior aspect. Over the fundus adjoining the upper end of the scar was a plum-coloured nodular mass 2·5 cm. × 2 cm. extending deeply into the substance of the uterine wall. Both ovaries were enlarged by multiple cysts. The lungs were studded over their surfaces with numerous rounded and raised subpleural haemorrhagic nodules, each 0·5 cm. to 0·75 cm. in diameter. On section, similar nodules were seen scattered throughout the substance of the lung, more towards the periphery. The brain showed an area of disruption in the left occipital lobe caused by a blood clot 3·5 cm. in diameter.

Histological sections of the uterus showed extensive infiltration of the myometrium by groups of trophoblastic cells which are especially found within the uterine veins (Fig. 6). Chorionic villi are present but are relatively scanty. Foci of necrosis associated with inflammatory reaction, presumably from necrotic tumour cells, are a prominent feature.

Section of the lung showed numerous rounded areas of haemorrhage with chorionic villi in several of these areas (Fig. 7). Sections of brain revealed no evidence of chorionic villi or trophoblastic metastases.

Discussion

The most arresting feature of this case is the rapidly fatal course of the disease, only seven weeks intervening between the first visit to hospital and death. Initially, the diagnosis was missed, although it was noted that the uterine size was larger than would be expected for the period of gestation. On the second admission, however, there was little doubt as to the

diagnosis when the full picture of a perforating mole was presented, namely, undue uterine enlargement with no signs of a foetus, internal haemorrhage, and bilateral cystic ovarian tumours.

A conservative approach was adopted at laparotomy as the patient was 19 years old and had only been recently married. However, within a month of her discharge from hospital, the patient was dead. Any discussion as to how the tragedy could have been averted remains a matter for speculation.

The pathological studies indicate that this is a case of malignant hydatidiform mole or chorioadenoma destruens, whether one follows the criteria laid down by Ewing (1910) or Novak and Seah (1954). Chorionic villi were present in both the hysterotomy and autopsy specimens of uterine muscle. The sections of lung indicate that there had been showers of villous emboli from the uterus, and presumably one or more emboli from the pulmonary foci had entered the systemic circulation to lodge in the brain, with subsequent cerebral haemorrhage and death.

Summary

These two cases are presented because of the many clinical and histological similarities yet the outcomes were very different. The presence of many well-formed villi in the second case both in the primary and secondary sites refutes the widely-held contention that such lesions do not give rise to metastases.

Acknowledgments

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A FURTHER CASE OF CHORIOANGIOMA

BY

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CHORIOANGIOMA is generally believed to be a benign tumour having origin in the chorionic mesenchyme. The literature, the aetiological and the pathological aspects of the condition have recently been reviewed by Shaw Dunn (1959). Hydramnios with premature labour and possibly dystocia have been the only clinical complications attributed to the tumour and in general it has no clinical significance. The present case is of interest in that foetal circulatory upsets were observed.

CASE REPORT

The mother was an extremely obese primigravida aged 21 years. Before pregnancy she weighed 15 stones, while at term she weighed 17½ stones. Her obesity made palpation and foetal heart recordings most inaccurate and at one point intra-uterine death was suspected.

The pregnancy was complicated by pre-eclampsia of a severity requiring hospitalization for eight days, at the thirty-third week. She was re-admitted in labour four weeks later. The amount of liquor was not remarkable when the membranes ruptured. Meconium-staining was noted and, after two hours in the second stage, mid-cavity forceps delivery was performed under local anaesthesia. An intramuscular injection of ergometrine maleate 0·5 mg. with hyalase was given as the head crowned. A live female child, which was limp and cyanosed and weighing 6 pounds 4 ounces (2·8 kilo) was born.

The cord was not divided for about two minutes and was noted to be long and markedly engorged. The placenta and membranes were expressed complete and then a firm tumour on the foetal aspect of the placenta adjacent to the cord insertion was noted. Blood loss amounted to 6 fluid ounces (170 ml.).

The infant cried shortly after birth but remained cyanosed. The cyanosis persisted for 72 hours and only then was the child removed from its oxygen environment. Within minutes of birth the liver edge was palpable at umbilical level but after 24 hours it was not palpable abdominally. Clinical examination of the chest revealed normal heart sounds but a chest X-ray (Fig. 4) taken twelve hours after birth suggested cardiac enlargement.

After this initial setback the baby has done well and when seen two months later was considered quite normal.

THE PLACENTA

The placenta was large, measuring 20×17 cm. and weighing 2½ pounds (1,134 g.). The umbilical cord was 36 inches (91·44 cm.) long. About one-fifth of the organ was occupied by a 9×9×6 cm. angioma (Fig. 1) which lay to one side of the insertion of the cord and projected from the foetal surface. This mass appeared to be partly encapsulated.

Microscopical examination confirmed a simple haemangioma composed of vessels (Figs. 2 and 3) which were in the main of capillary dimensions. A few of the larger channels contained thrombi. In the remainder of the placenta there was a slight excess of fibrin deposited chiefly under the amnion with a good deal of calcification.

Discussion

It is postulated that overloading of the venous circulation at birth from the excess pool of blood lying in capillary spaces of the angioma would account for this child's condition. The temporary cyanosis, hepatic and cardiac enlargement lend support to this view. Probably also, due to high venous pressure there was delayed closure of the ductus arteriosus, thus accentuating the cyanosis.

This clinical aspect of chorioangioma has not previously been reported though Russell (1956) investigated his case a few weeks from birth and found no heart enlargement.

It is suggested that early clamping of the umbilical cord in cases where it is noted to be extremely engorged will prevent circulatory overloading. The problem, however, is a minor one due to the extreme rarity of chorioangiomata of significant size. This is the first case to be observed in this hospital in the past 5 years, i.e., an incidence of 1 in 11,000 deliveries.

Acknowledgments

Acknowledgments are due to Dr. R. de Soldenhoff, County Obstetrician, Dr. Alan Abramson, County Paediatrician and Dr. J. A. Milne, County Pathologist, for assistance in reporting this case.

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FIG. 1
Placenta showing chorioangioma on foetal aspect.

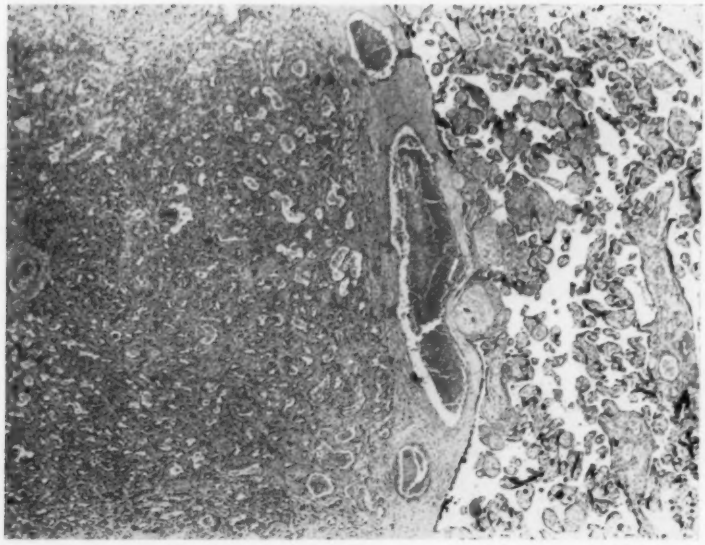

FIG. 2
Microscopic section showing chorioangioma and capsule with adjacent placental villi. ×10.

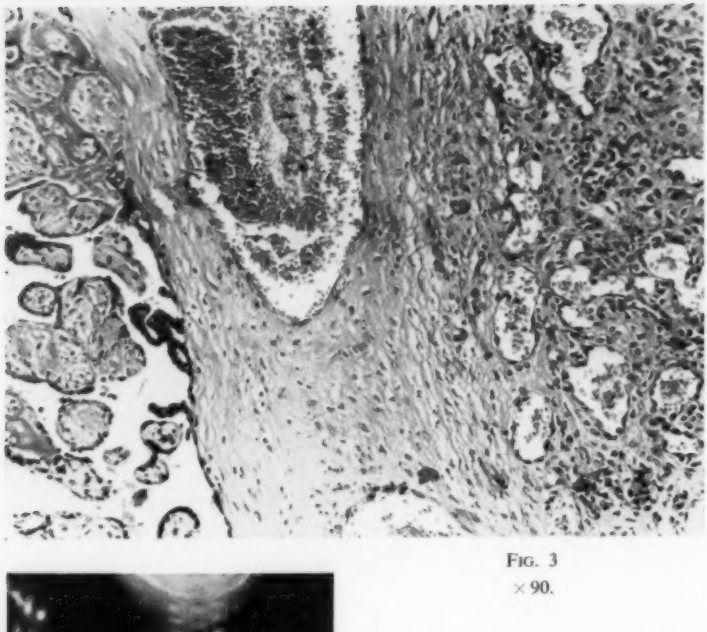

FIG. 3
×90.

FIG. 4
Chest radiogram taken shortly after birth, showing cardiac enlargement.

HYDATIDIFORM MOLE WITH CO-EXISTENT FOETUS

BY

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THE association of a foetus together with hydatidiform degeneration of the placenta is an uncommon one in clinical obstetrical experience. The following series is presented to record further examples of this condition, and to illustrate various modes of presentation, together with the problems which may be encountered in their management.

At the Royal Women's Hospital during the 20-year period from 1940 to 1959 inclusive, there were 110,477 patients delivered, and 32,358 patients treated for abortion. In this interval 261 patients received treatment for hydatidiform mole, and there were 10 patients with hydatidiform mole and co-existent foetus. The incidence in this hospital of hydatidiform mole with foetus is therefore approximately one in 14,000 pregnancies. Bowles (1943) reported the incidence of a single ovum with hydatidiform mole and co-existing foetus as one in 9,501 pregnancies, at the Queen's Hospital, Honolulu. Williams (1918) stated that no instance of a viable foetus, together with hydatidiform formation of the placenta, had been found in 17,930 obstetrical cases treated in the Johns Hopkins Hospital.

During the period reviewed 104 specimens of hydatidiform mole, and 5 of mole with associated foetus, were referred for examination to the Department of Pathology by private practitioners. This series therefore comprises 15 cases of hydatidiform mole and associated foetus, 10 occurring in Royal Women's Hospital patients, and 5 in referred material.

There were in addition to these 15 cases a further 5 in which hydatidiform mole with co-existent foetus was diagnosed on questionable microscopic evidence. These have been excluded from the series, however, for the degenerative changes in the chorionic villi fell short of those seen in true hydatidiform mole. In cases where placental tissue has become fibrotic prior to expulsion from the uterus, early hydropic change and avascularity of villi are of doubtful significance. Such cases are best regarded as potential moles, and whilst they warrant the customary clinical surveillance they should be classified separately, for their pathology is conjectural. These appearances indicate that true hydatidiform changes might have occurred had the chorionic villi remained longer within the uterus.

Meyer (1918) demonstrated that the incidence of hydatidiform degeneration of the placenta is considerable when all abortuses are examined histologically. However, the combination of a foetus with a macroscopic hydatidiform mole remains a rare one, and it is this clinical condition with which this paper is mainly concerned.

At the Royal Women's Hospital it is not a routine procedure to examine all abortuses microscopically, and only macroscopically abnormal material is referred for further examination. Of the 365 hydatidiform moles seen during the 20-year period reviewed, 118 (32·3 per cent) were diagnosed by microscopic appearances, and in this group are included 16 cases of ectopic gestation.

In the series presented 12 of the 15 cases showed macroscopic evidence of hydatidiform mole with typical vesicular appearance of the placenta, whilst in the remaining 3 cases the diagnosis was made by histological examination.

Clinical Summaries

Case 1

Mrs. B., a nullipara aged 24 years, had episodes of vaginal bleeding throughout the antenatal period. A spontaneous breech delivery occurred at 26-weeks gestation, the male foetus being born alive but surviving for only 12 hours.

Figure 1 illustrates the placenta, which appeared normal except for the mass of molar tissue replacing one cotyledon.

Case 2

Mrs. X, aged 26 years, had had four previous normal confinements. Intermittent vaginal bleeding occurred during the early months of the present pregnancy. Disproportionate uterine enlargement was noticed at 20-weeks gestation, and multiple pregnancy was diagnosed. The pregnancy then proceeded uneventfully until bleeding re-occurred at 36-weeks gestation. Spontaneous premature labour followed, and a living male infant weighing 5 pounds 10 ounces was delivered by forceps.

Two masses (Fig. 2) then appeared spontaneously at the vulva, one being a normal placenta, and the other a separate mass with the vesicular structure of a hydatidiform mole. Microscopically the molar tissue appeared necrotic, and showed no evidence of trophoblastic activity.

Case 3

Mrs. S., a primigravida aged 19 years, came into spontaneous premature labour at 31-weeks gestation, and was delivered of a living female infant weighing 3 pounds 4 ounces. Prior to the onset of labour the patient had received treatment for mild pre-eclampsia.

The placenta showed diffuse vesicular degeneration on macroscopic inspection (Fig. 3), and sections showed the characteristic structure of a hydatidiform mole in some areas (Fig. 4), whilst in others the structure was that of normal mature placental tissue. In some areas trophoblastic activity was marked.

Case 4

Mrs. D., after an uneventful antenatal period, came into spontaneous labour at 39-weeks gestation. An assisted breech delivery ensued and resulted in a living infant weighing 6 pounds 8 ounces. A normal placenta was then delivered and this was followed by a separate mass of vesicular tissue, sections of which revealed the typical appearance of a hydatidiform mole.

Case 5

Mrs. S., a nullipara aged 25 years, had an uneventful antenatal course until after 24-weeks amenorrhoea when it was noted that the uterine size had remained stationary for four weeks. Foetal movements had not occurred. At 25-weeks gestation a spontaneous abortion occurred of the conceptus shown in Figure 5. The foetus was a female.

Sections through the placental tissue confirmed the diagnosis of hydatidiform mole. Many of the villi were fibrotic and showed the regressive changes which are seen in a missed abortion.

Case 6

Mrs. W., aged 21 years, had had three previous normal confinements. She presented at 16-weeks gestation with severe vaginal bleeding which necessitated blood transfusion. Shortly after admission a spontaneous abortion occurred of the foetus and molar tissue shown in Figure 6. Sections showed the structure of a typical hydatidiform mole, with some, but not excessive, trophoblastic proliferation.

Case 7

Mrs. D., aged 32 years, had had two previous normal confinements. The antenatal course was uneventful until slight vaginal bleeding occurred at 16-weeks gestation. Thereafter the uterus failed to enlarge and at 20-weeks gestation it had diminished in size, and the Toad pregnancy test was negative. Dilatation and curettage was then performed, and the material shown in Figure 7 was obtained.

The foetus was only 15 millimetres in length, and microscopic examination revealed that most of the hydatidiform mole tissue had undergone fibrous degeneration.

Case 8

Mrs. G., aged 22 years, had in her only previous pregnancy been delivered of a living infant at term, by classical Caesarean section, performed because of pelvic contraction. In this pregnancy she had required treatment for hyperemesis gravidarum since early in the second month. At 16-weeks gestation she was admitted to hospital because of severe pre-eclampsia. The uterus was enlarged to the size of a 28-weeks pregnancy, but no foetal parts were palpable. The blood pressure was 160/90 millimetres of mercury, and the urine contained 24 grams of albumin per litre. Marked generalized oedema was present. X-ray of the abdomen revealed a very small foetal skeleton and disproportionate uterine enlargement. The Aschheim-Zondek test was positive, but negative in dilutions. The diagnosis of hydatidiform mole with foetus was made, and in view of the severe pre-eclampsia the pregnancy was terminated by abdominal hysterotomy. The patient thereafter had an uneventful convalescence. Figure 8 illustrates the foetus within an intact hydramniotic sac, together with the hydatidiform mole tissue removed at operation. The foetus was a female and had abnormalities of the face and neck and also a lumbosacral myelocele.

Case 9

Mrs. M., a nullipara, aged 24 years, was admitted to hospital at 11-weeks gestation with hyperemesis gravidarum, which responded to treatment with intravenous fluids. At 16-weeks gestation the patient was re-admitted because of pre-eclampsia. The uterus was enlarged beyond the period of gestation, and felt doughy

N.A.B. [232]

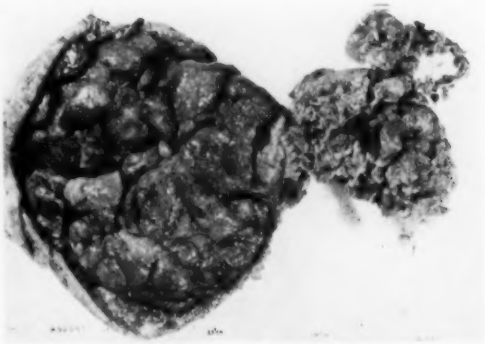

FIG. 1

Hydatidiform degeneration in a single cotyledon of an otherwise normal placenta.

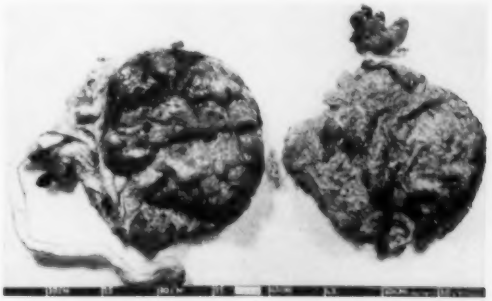

FIG. 2

Twin pregnancy. Normal placenta with separate mass of necrotic hydatidiform mole tissue. Period of gestation 36 weeks. The infant survived.

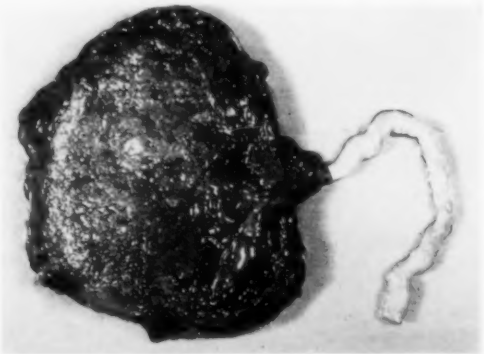

FIG. 3

Placenta showing diffuse vesicular degeneration. Spontaneous delivery at 31-weeks gestation; infant survived.

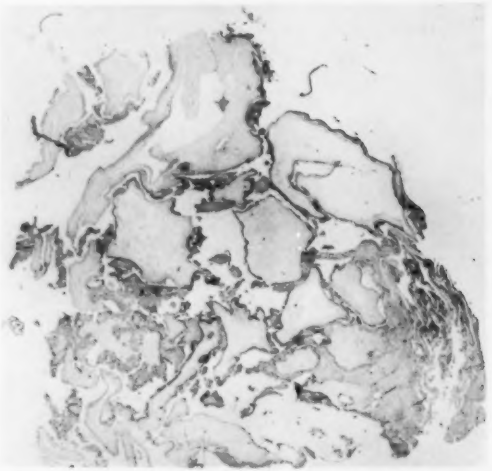

FIG. 4

Section of the placenta shown in Figure 3. The villi are greatly enlarged, hydropic and avascular. Negative made by direct contact from section. H. and E. ×4.

FIG. 5

Necrotic hydatidiform mole with macerated foetus. Foetal death *in utero* 5 weeks prior to abortion.

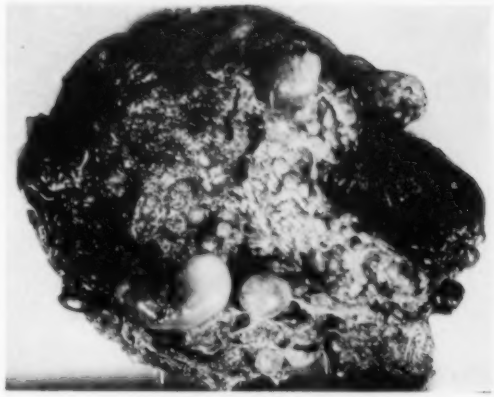

FIG. 6

Hydatidiform mole with embryo only 3 cm. in length. Period of gestation 16 weeks.

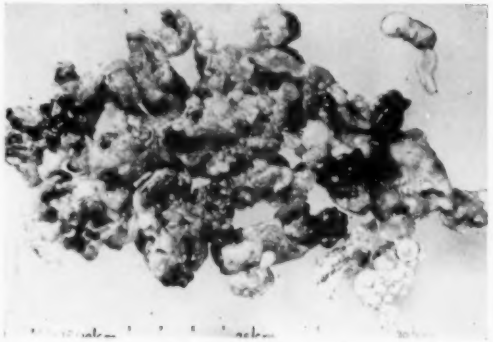

FIG. 7

Missed abortion diagnosed at 16-weeks gestation. Embryo and hydatidiform mole evacuated by curettage.

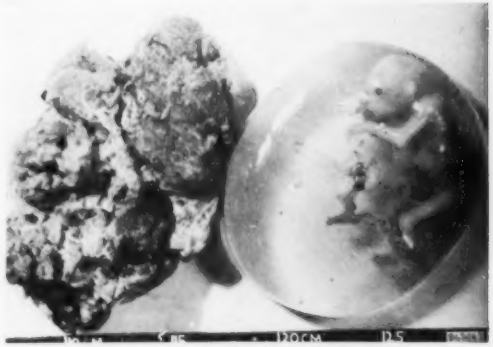

FIG. 8

Hydatidiform mole tissue and grossly abnormal foetus within an intact hydramniotic sac. Hysterotomy performed at 16-weeks gestation.

and hydatidiform mole evacuated by curettage.

an intact hydramniotic sac. Hysterotomy performed at 16-weeks gestation.

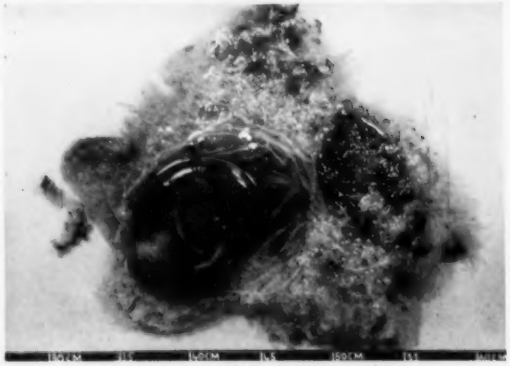

FIG. 9

Normally developed female foetus and hydatidiform mole. Period of gestation 18 weeks at the time of hysterotomy.

FIG. 10

Hydatidiform mole and macerated male foetus. Period of gestation 16 weeks at the time of hysterotomy.

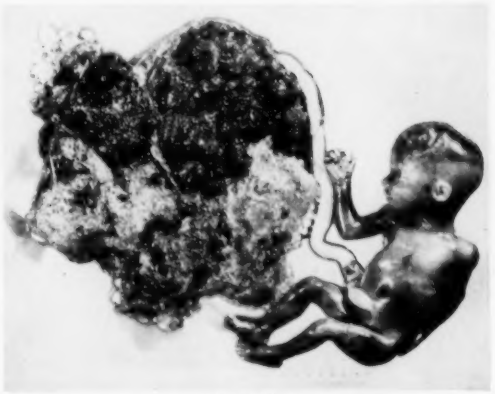

FIG. 11

Hydatidiform degeneration of part of a single placenta. The period of gestation was 25 weeks at the time of delivery. The foetus was a male and survived for 10 minutes.

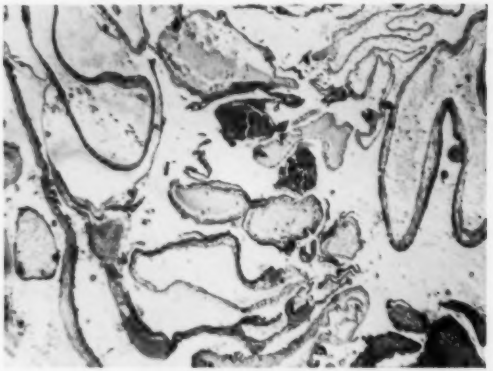

FIG. 12

Section showing the typical features of a hydatidiform mole. Case 12. H. and E. ×22.

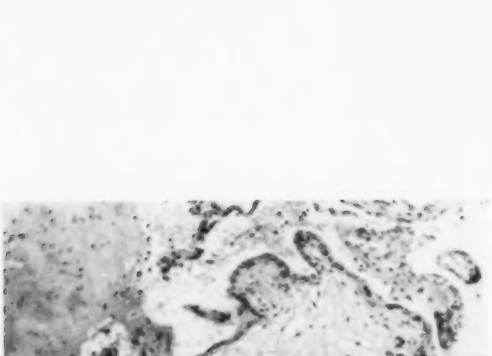

FIG. 13

Section of the placenta from Case 14, showing an enlarged avascular chorionic villus. H. and E. ×75.

on palpation. An Aschheim-Zondek test was positive at a 1 in 200 dilution. X-ray revealed a very small foetal skeleton, and a disproportionately large uterine soft tissue shadow.

Hydatidiform mole with co-existent foetus was diagnosed, and when the pre-eclampsia became worse in spite of treatment, an abdominal hysterotomy was performed. Figure 9 illustrates the hydatidiform mole tissue and normally developed female foetus which were removed at operation.

Case 10

Mrs. H., aged 24 years, had had one previous normal confinement. In this pregnancy she was first admitted to hospital at 14-weeks gestation with hyperemesis gravidarum. She was re-admitted at 16-weeks gestation due to rapid enlargement of the abdomen, associated with severe headache and excessive weight gain. The blood pressure was 170/95 millimetres of mercury, and the urine contained 22 grams of albumin per litre. X-ray revealed a foetus whose size corresponded to that of a 16-weeks gestation, but the uterine size was equivalent to that of a 24-weeks pregnancy. The Aschheim-Zondek test was positive in a dilution of 1 in 1,000. Renal function tests revealed a total urea excretion of 50 per cent of average normal. The provisional diagnosis was choriocarcinoma. An abdominal hysterotomy was performed four days following admission, when the pre-eclampsia failed to respond to treatment. Figure 10 shows the male foetus and hydatidiform mole removed at operation.

Case 11

Miss W., a nullipara, aged 17 years, first presented with a threatened abortion at 18-weeks gestation, and gave a history of intermittent vaginal bleeding during the preceding 4 weeks. The blood pressure was 155/100 millimetres of mercury and "Serpasil" was prescribed. At 23-weeks gestation the patient was admitted to hospital, as the vaginal bleeding had continued, and because the height of the fundus corresponded to that of a 32-weeks pregnancy. Foetal movements had been noted by the patient for 4 weeks. X-ray revealed a single foetal skeleton corresponding to about 22-weeks gestation, and disproportionate uterine enlargement.

Aschheim-Zondek and Toad tests were positive in dilutions to 1 in 100, but negative at 1 in 200. Hydatidiform mole with associated foetus was diagnosed. Two weeks later abdominal pain and tenderness developed, and spontaneous labour commenced together with the onset of severe vaginal haemorrhage. An intravenous oxytocic drip was commenced and although this controlled the bleeding a blood transfusion was also instituted. Four hours later a speculum examination showed an almost fully dilated cervix, plugged with protruding molar tissue. The patient was anaesthetized, and 22 ounces of molar tissue was removed through the cervix, by means of sponge forceps. The intact amniotic sac then palpable was ruptured, and the foetus delivered by breech extraction.

The foetus, which was a normally developed male weighing 570 grams, succumbed 10 minutes after delivery. Figure 11 shows the foetus and hydatidiform degeneration in the portion of what appeared to be a single placenta.

Case 12

Mrs. R., aged 23 years, was first seen at 6-weeks gestation complaining of nausea and vomiting. As there had previously been two consecutive first trimester abortions, corpus luteum hormones were given, when urinary pregnanediol estimations revealed persistently low levels. The pregnanediol excretion failed to increase with this treatment, and the patient aborted at 13-weeks gestation.

The abortus consisted of a macerated foetus three centimetres in length, with placental tissue containing vesicles suggestive of a hydatidiform mole. This diagnosis was confirmed by microscopic examination of sections through the placental tissue—Figure 12.

Case 13

Mrs. G., aged 29 years, had previously had one normal confinement. In this pregnancy she presented at 10-weeks gestation and aborted soon after her admission to hospital. The embryo was seven millimetres in length, and, as the placenta appeared fibrous, it was referred for microscopic examination. Sections revealed patchy fibrosis of the placental tissue, and many villi were large, hydropic and avascular. Trophoblastic activity was minimal.

Case 14

Mrs. R., aged 26 years, had previously had one normal confinement. In this pregnancy a missed abortion was diagnosed at 10-weeks gestation, when two successive examinations at four-weekly intervals showed that the uterus was only slightly enlarged, and of static dimensions. Dilatation and curettage was performed, and the curettings were referred for microscopic examination. Sections showed portions of a small foetus, and placental tissue with large and avascular villi—Figure 13.

Case 15

Mrs. C., aged 24 years, had previously had four successive spontaneous first trimester abortions. She was initially seen at 6-weeks gestation, and the pregnancy proceeded uneventfully until spontaneous abortion occurred at 13-weeks gestation. Weekly urinary pregnanediol estimations had revealed normal pregnanediol excretion. The embryo had a crown rump measurement of 1·6 centimetres, and sections through the placental tissue showed the features of a hydatidiform mole.

Discussion

Foetal Sex

The sex of the foetus was recorded in 7 cases In Cases 3, 5, 8 and 9 the foetuses were females

and in Cases 1, 10 and 11 the foetuses were males. In Case 11 the foetus showed multiple abnormalities, but the other 6 appeared normally formed, although maceration was evident in Cases 5 and 10.

The foetuses in Cases 6, 7, 12, 13, 14 and 15 were too small for macroscopic identification of genital sex, and in the twin pregnancies of Cases 2 and 4, the molar placentae had no associated foetuses.

Park (1960) has stressed the academic importance of sex determination in such pregnancies, and on his suggestion it is proposed to investigate and report upon the nuclear sex of the trophoblast in all 15 cases, and also of the foetuses which were preserved.

Age and Parity

The average age of the patients in this series was 24 years, and 7 were nulliparous, although 2 of these had previously had first trimester abortions.

Gestation at Delivery

The average period of gestation at delivery was 21·3 weeks. In only three cases did the pregnancy proceed beyond the 28th week and these provided the three surviving infants. There were in addition two neonatal deaths of pre-viable foetuses.

Modes of Presentation and Delivery

(1) *Spontaneous Abortion—Four Cases*

All of the patients in this group were clinically uneventful until the onset of abortion, which in one patient was accompanied by profuse vaginal bleeding.

(2) *Missed Abortion—Three Cases*

Dilatation and curettage was performed in two of these patients, while the other aborted spontaneously, four weeks after the diagnosis of foetal death *in utero* had been established.

(3) *Vaginal Bleeding—Three Cases*

In Case 1 vaginal bleeding occurred intermittently throughout pregnancy and delivery was spontaneous and uneventful.

In Case 2 vaginal bleeding ceased after the 20th week at which time death of the hydatidiform mole presumably occurred. The bleeding which re-occurred prior to the spontaneous delivery at 36 weeks, was probably due to a mild accidental haemorrhage associated with the "normal" placenta—Figure 2.

This interpretation explains the unusually advanced gestation for a hydatidiform mole, and is supported by the histological appearances of necrosis and lack of trophoblastic activity seen in the molar tissue.

In Case 11, vaginal bleeding, which was initially intermittent and mild, became severe after the onset of labour, and was controlled by an intravenous oxytocic drip. Delivery was achieved by breech extraction. This patient required five pints of blood during and after delivery.

(4) *Pre-eclampsia—Four Cases*

Cases 8, 9, 10 first presented with hyperemesis gravidarum which necessitated admission to hospital. All three subsequently developed severe pre-eclampsia at 16 to 18-weeks gestation, and it was not until then that the diagnosis of hydatidiform mole was first considered.

The X-ray in these three patients showed uterine enlargement out of proportion to the size of the foetal skeleton, which was smaller than the gestational age in two of them. The Aschheim-Zondek test was positive in dilutions in two of the three patients, and all were delivered by hysterotomy, when the pre-eclampsia failed to improve with treatment.

The final patient (Case 3) in this group presented with mild pre-eclampsia, and a spontaneous delivery at 31-weeks gestation resulted in a living premature infant.

(5) *Spontaneous Full-time Delivery—One Case*

Case 4 was one of twin pregnancy in which hydatidiform degeneration had occurred in one placenta. The necrotic changes seen in the molar tissue explain the absence of toxic symptoms, and the advanced period of gestation at delivery.

Diagnosis

The problem of diagnosis is a very real one unless molar tissue has spontaneously appeared *per vaginam*. The uterus may have a doughy consistency when palpated, and foetal movements and heart sounds may or may not be detectable. Investigations which are so useful in the diagnosis of a hydatidiform mole lose much of their value when the mole is associated with a demonstrable foetus. Correct diagnosis is of greater importance in those patients who present with ante-partum haemorrhage or pre-eclampsia, rather than in those presenting with a threatened or missed abortion. In this series there were 7 patients in each of these two categories.

When hydatidiform mole and foetus co-exist the X-ray not only fails to provide diagnostic assistance, but leads to clinical confusion. The presence of a foetal skeleton persuades one against a diagnosis of hydatidiform mole, especially as the excessive uterine enlargement is radiographically indistinguishable from hydramnios.

Quantitative determinations of chorionic gonadotrophin in the urine can be of great assistance, and in Cases 9 and 11 it was largely due to this investigation that correct diagnosis was possible prior to evacuation of the molar tissue.

The passage of a uterine sound to confirm the diagnosis of hydatidiform mole is, as Acosta-Sison (1958) has emphasized, contra-indicated when the presence of a foetus is suspected.

The differential diagnosis of hydatidiform mole with foetus is that of the acute form of hydramnios occasionally associated with multiple pregnancy, abnormal foetus, diabetes and erythroblastosis. The alternatives are the other rare causes of fulminating second trimester pre-eclampsia, such as essential hypertension and chronic nephritis. Choriocarcinoma also merits consideration when the urinary gonadotrophin titre is grossly elevated.

With the exception of choriocarcinoma the precise diagnosis is mainly of academic interest, for such cases offer no alternative to immediate termination of the pregnancy, for the foetus does not merit consideration. Choriocarcinoma provides an exception, not as regards the decision to terminate the pregnancy but as to the route selected and the scope of initial surgery. Choriocarcinoma was the pre-operative diagnosis in Case 10, and it is of interest that this condition is more common than that of hydatidiform mole with co-existent foetus; 17 cases occurring during the 20-year period reviewed, an incidence of 1 in 6,500 pregnancies.

Treatment

The patients who presented with incomplete or missed abortions were treated by curettage, and in this group the diagnosis was not established until after the molar tissue had been evacuated.

It is in the group of patients with severe pre-eclampsia that the question arises as to the most suitable means of termination. Cases 8, 9 and 10 were treated by abdominal hysterotomy, which was then the current practice at the Royal Women's Hospital for the evacuation of hydatidiform moles.

MacRae (1959) and McKelvey (1959) have emphasized that intravenous oxytocics have obviated the need for hysterotomy in cases of hydatidiform mole. Once the cervix reaches adequate dilatation, vaginal evacuation of the mole may be performed with sponge-holding forceps. During the procedure the oxytocic drip is continued, and 0·5 milligram of ergometrine given by intravenous injection to ensure a tense uterine wall, for this minimizes bleeding and reduces the risk of uterine perforation. It is advisable to commence blood transfusion prior to evacuation. Case 11 was managed by this regime which would however have been contra-indicated in Case 8 where the patient had had a previous classical Caesarean section. Also choriocarcinoma, which was the pre-operative diagnosis in Case 10, provides a special contra-indication to intravenous oxytocics, which might cause dissemination of malignant cells throughout the maternal circulation.

All patients with hydatidiform mole and associated foetus require continued clinical observation and gonadotrophin estimations in order that prompt recognition and early institution of treatment be possible should choriocarcinoma supervene.

Gross Pathology

This series of cases illustrates four different circumstances in which hydatidiform mole occurs in association with a foetus.

(1) Partial degeneration of a single placenta. Cases 1 and 11. Survival of the foetus in this group is dependent upon a sufficient mass of normal functioning placenta, and upon the activity of that part which is molar for that is what determines the duration of the pregnancy.

(2) Complete degeneration of one of twin placentae. Cases 2 and 4. The survival of the opposite twin is dependent upon the death of the hydatidiform mole, without which the pregnancy will fail to reach viability.

(3) Diffuse degeneration of a single placenta. Case 3. A review of the literature indicates that this case of diffuse hydatidiform degeneration of a single placenta, with survival of the infant, is unique; other reported cases of hydatidiform mole with associated living infants belonging to the above two groups.

(4) Complete hydatidiform degeneration of a single placenta. The remaining 10 cases belong in this category. The disparity between the size of the foetus and the period of gestation seen in these cases, indicates that foetal death usually precedes delivery by some weeks. That these hydatidiform changes precede and cause foetal death can be inferred from the cases quoted, in which, in spite of extensive hydatidiform degeneration of the single placentae, normally developed infants were born alive.

Hydatidiform moles therefore do not represent mere degenerative changes, subsequent to retention of chorionic villi in the uterus, after foetal death has occurred. Also, the size attained by these foetuses belies any aetiological explanation which relates to a complete primary failure in development of foetal blood vessels within the chorionic villi. These inferences disagree with those of Nesbitt (1957) who states that a hydatidiform mole is derived from a true pathologic ovum, in which the embryo is either absent or very defective from the beginning.

As the hydatidiform changes involve the placental villi the life of the foetus becomes imperilled. The size which the foetus attains is dependent upon the stage of gestation at which the hydatidiform change commences, and also upon the rate of its progression and the amount of the placenta involved. The degree of trophoblastic over-activity probably determines the manifestations of pre-eclampsia, since it is in these cases (9 and 10) that the chorionic gonadotrophin content of the urine is elevated. This in turn determines the gestation at delivery, for termination becomes inevitable once severe pre-eclampsia develops.

Summary

(1) Fifteen cases of hydatidiform mole with associated foetus are discussed, with emphasis on the various modes of presentation, and the methods of delivery.

(2) A case of diffuse hydatidiform degeneration of a single placenta, with survival of the infant, is recorded.

(3) Four gross pathological varieties of hydatidiform mole are discussed, with reference to the different clinical patterns which accompany them.

(4) It is deduced from the material quoted, that hydatidiform change is not merely degeneration dependent upon death or developmental failure of the foetus.

(5) The foetus associated with molar change in a single placenta may be either male or female.

Acknowledgments

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THE CLEARANCE OF RADIOACTIVE SODIUM FROM THE MYOMETRIUM OF THE PREGNANT DIABETIC

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INTRODUCTION

IT is well established that pregnancy complicated by maternal diabetes is associated with a higher stillbirth and neonatal death rate than normal. The reason for this is not clear although from the clinical point of view improved results can only be obtained by careful control of the maternal diabetes during the pregnancy. It was thought possible on theoretical grounds that a failing maternal placental circulation might be responsible for some of the foetal losses and as part of an investigation into placental function in the diabetic it was decided to study the rate of clearance of radioactive sodium (^{24}Na) from the myometrium during the latter part of pregnancy in diabetics.

Measurement of the rate of clearance of ^{24}Na from tissues as a measure of their effective blood supply was first described by Kety (1948, 1949). Since then the method has been applied to the myometrium in pregnant patients by Morris *et al.* (1955, 1956), Johnson and Clayton (1957) and Moore and Meyerscough (1957). These authors have found that the effective blood flow in the uterine wall is decreased in patients suffering from pre-eclampsia, during exercise (Morris *et al.*) and in postmature primigravidae (Moore and Meyerscough). They have concluded that in these conditions the maternal placental blood flow is reduced *pari passu* with the reduction in myometrial blood flow. It would seem therefore that there is a level of myometrial blood flow below which the maternal placental circulation becomes insufficient for the requirements of the foetus and intra-uterine foetal death then ensues. This is the explanation offered for intra-uterine death occurring in severe pre-eclampsia and in postmaturity. The present investigation was designed to see whether a similar set of circumstances arose in the pregnant diabetic.

MATERIAL

Measurement of the ^{24}Na myometrial clearance rate was made in 68 diabetic and 26 non-diabetic patients. In the non-diabetics only one estimation was made, usually at, or about, 40 weeks. In the diabetic patients, however, a clearance test was carried out shortly after their admission for rest and stabilization at 32 weeks and this was repeated 2 weeks later. Where possible, a third test was carried out 4 weeks after the initial test. Of the 68 diabetics, 38 had

2 tests performed, 19 had 3 tests and in 2 patients 4 tests were performed because the patients were admitted before 32 weeks. In 9 patients delivery took place after only 1 estimation had been made.

Amongst the 26 non-diabetic patients there were 7 who were suffering from mild pre-eclampsia (as defined by Morris *et al.*, 1955) at the time that the test was performed, whilst 16 of the 68 diabetic pregnancies were similarly complicated. Hydramnios occurred in 28 of the diabetics and 8 of these also suffered from pre-eclampsia. There were 4 stillbirths and 5 neonatal deaths amongst the diabetics and there were 4 cases of neonatal "pulmonary syndrome" with survival. There were no stillbirths or neonatal deaths in the non-diabetic group. The distribution of the various subgroups is shown in Table I.

TABLE I

	Total Number of Cases	Number of Stillbirths, Neonatal Deaths, or Pulmonary Syndromes
Non-Diabetic:		
Normal	19	0
Pre-eclampsia	7	0
Diabetic:		
Uncomplicated	22	0
Pre-eclampsia	5	0
Hydramnios	30	10
Pre-eclampsia and hydramnios	11	3
Total	94	13

METHOD

The method of performing the ^{24}Na clearance test was similar to that described by Morris *et al.* (1955). A dose of 0·4 ml. of isotonic ^{24}Na Cl solution containing 10 microcuries per ml. was injected into the myometrium at a point just below and to the right of the umbilicus. The centre of the counting tube (A G4Pb with 1 cm. lead shielding and a collimation slit 1 cm. wide along its whole length) was placed over the injection site. The tube was fitted with perspex "wings" which projected 10 cm. on either side of the tube and were curved to the shape of the abdomen. These served to steady the tube which was secured in position with strips of Sellotape. The weight of the tube was largely supported by counterweight mounting of the angle poise variety. A rate-meter and pen-recorder were used to follow the clearance rate. The pen-recorder curve was subsequently replotted on semi-log paper and after a background correction had been made the clearance time to half value, $t\frac{1}{2}$, was read off (Fig. 1). In 118 plots the curve was a straight line (Fig. 1a)

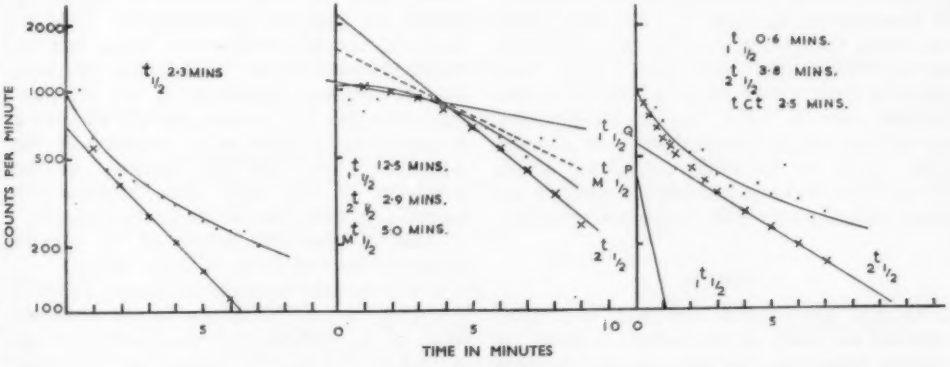

FIG. 1 a, b, c

Forms of curves observed before and after the subtraction of the rising body background.

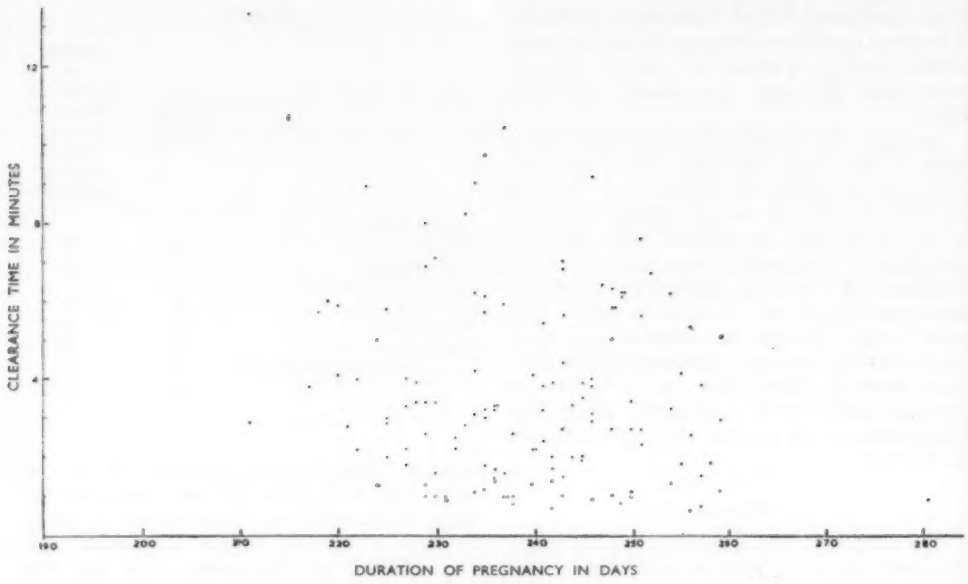

FIG. 2
The effect of duration of pregnancy on the clearance time.

and the clearance time could be read off directly. In the remaining 65 plots a 2 component curve was present (Fig. 1 b, c) and in these cases a mathematical mean (the total clearance time or T.C.T.) of the 2 components was calculated as described in the Appendix. No explanation was found for the 2 component curve but there was no evidence that some patients were more prone to have it than others. Furthermore, the average value of T.C.T. for the 2 component curves was almost identical with the average value of $t\frac{1}{2}$ for the single component curves so that there were no grounds for rejecting the results calculated from the 2 component curves.

RESULTS

As has been stated clearance tests were repeated on many of the diabetic patients. A striking feature was the large variation between these determinations on the same patient: for instance the mean difference for the patients from whom 2 values were obtained was 2·28 minutes. Nevertheless it can be shown that the variance between patients was significantly greater than that within patients or, in other words, there was a real measure of uniformity among the repeated determinations. Furthermore, as shown in Figure 2, there was no detectable trend in the value of the clearance time as pregnancy advanced. It was therefore concluded that the average value of successive determinations was a valid measure of the response of an individual patient. In the remainder of this paper such averages are treated as if they were single determinations.

Table II gives the results of the present investigations and those of other series.

It will be seen from Table II and Figure 3 that there was no difference in the clearance times of the diabetic and non-diabetic groups as a whole and that furthermore the occurrence of mild pre-eclampsia did not have an adverse effect either in the small number of non-

TABLE II

Author	Type of Patient Examined	Number of Cases	Mean Clearance Time	S.E.	Significance of Difference
Morris *et al.*, 1955	Normal	20	4·1	0·35	
	Mild pre-eclampsia	10	7·7	0·52	
	Severe pre-eclampsia	8	15·3	2·85	
Johnson and Clayton, 1957	Normal	14	4·7	0·33	
	Mild pre-eclampsia	8	8·14	1·45	
	Severe pre-eclampsia	11	11·6	1·1	
Moore and Meyerscough, 1957	Normal	40	6·5	0·56	
	Pre-eclampsia	47	8·3	0·58	
Present Series, 1960	Non-diabetics	26	3·29	0·45	Not significant
	Diabetics	68	3·75	0·28	
	Non-diabetics:				
	Normal	19	3·46	0·59	Not significant
	Mild pre-eclampsia	7	2·81	0·58	
	Diabetics:				
	No pre-eclampsia	52	3·77	0·33	Not significant
	Mild pre-eclampsia	16	3·71	0·54	
	No hydramnios	27	3·79	0·36	Not significant
	Hydramnios	41	3·72	0·40	
	Infant survived	59	3·92	0·31	Not significant
	Infant stillborn	4	3·05	1·11	
	Infant survived, no pulmonary syndrome	55	3·98	0·32	Not significant
	Infant survived after pulmonary syndrome	4	3·0	1·0	
	Infant survived	59	3·92	0·31	Significant at 5%
	Infant died after delivery	5	2·38	0·63	
	Infant survived	59	3·92	0·31	Not significant
	Infant stillborn or died after delivery	9	2·68	0·57	
	Infant survived, no pulmonary syndrome	55	3·98	0·32	Significant at 5%
	Infant stillborn or died after delivery or had pulmonary syndrome	13	2·78	0·48	

NOTE:—Significance was assessed by the "t" test.

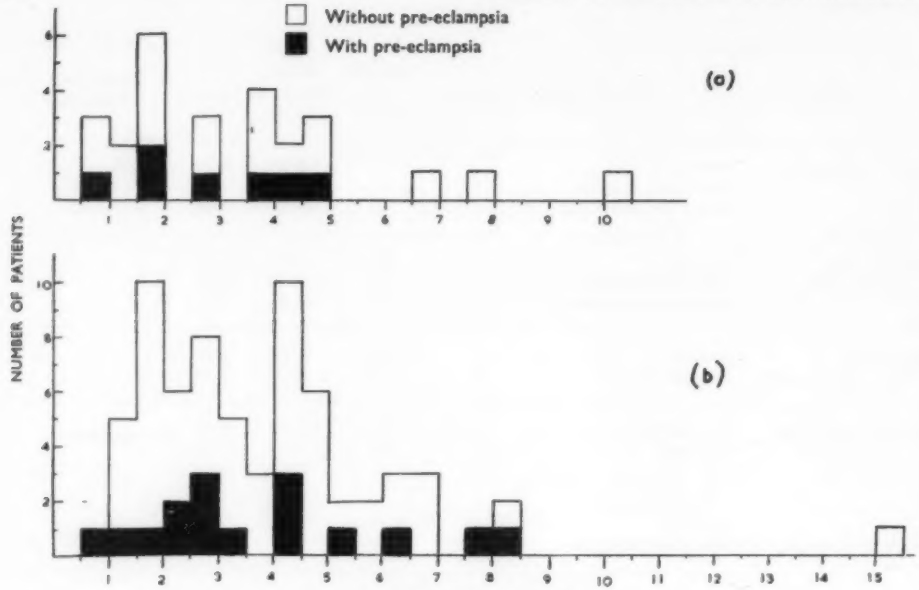

FIG. 3

Comparison of (a) and (b) shows the distribution of clearance times in normals and diabetics with and without pre-eclampsia.

diabetics studied or in the larger number of diabetics. Hydramnios was present to a varying degree in 41 of the diabetic patients but did not adversely affect the mean clearance time. On considering the association between the fate of the foetus and the mean clearance time it was found that the "affected infant" group of diabetics (stillbirth, neonatal death or pulmonary syndrome) as a whole had a significantly *faster* time, implying an increased myometrial blood flow, than the group of diabetics whose infants survived uneventfully. On further analysis it was seen that the mean clearance time of the diabetics in whom the baby died *in utero* or shortly after birth was faster than in those in whom the baby survived (including those recovering from the pulmonary syndrome). This difference however fell just short of significance at the 5 per cent level. The neonatal death group alone had a significantly faster clearance time than the group where the infant survived but the stillbirth and pulmonary syndrome groups alone did not show this difference.

Table III shows the relationship of the clearance time to various maternal factors.

(a) *Maternal Age*

In considering the effect of increasing age on myometrial blood flow in the diabetic patients a trend was noted toward slower clearance times with increasing age. On statistical analysis this relationship fell just short of significance at 5 per cent level.

(b) *Age of Onset and Duration of Diabetes*

No correlation was found between the age of onset or the number of years that the patient had been a diabetic and the clearance time.

TABLE III

Diabetics Only: Correlation Between Clearance Time and Maternal Factors

Correlation Between Clearance Time and Maternal Factors	Correlation Coefficient	Significance of Correlation Coefficient
Age of patient	0·19	Not significant
Age of onset of diabetes	0·04	Not significant
Duration of diabetes	0·08	Not significant
Dose of insulin at start of pregnancy	−0·19	Not significant
Change of insulin dose during pregnancy	−0·12	Not significant
Dose of insulin at end of pregnancy	−0·22	Significant at 5%
Initial weight of patient	0·01	Not significant
Weight increase during pregnancy	−0·004	Not significant
Final weight of patient	+0·004	Not significant

(c) *Insulin Dosage*

A significant negative correlation was evident with the insulin dose necessary at the end of the pregnancy; it was found that higher insulin dosage was associated with a more rapid clearance time. The correlation at the onset of pregnancy was not quite significant.

(d) *Initial Weight, Final Weight and Weight Gain During Pregnancy*

None of these factors appeared to have any consistent effect upon the clearance time.

DISCUSSION

Delaying delivery beyond the 37th week would only be justifiable if it was reasonably certain in each individual case that intra-uterine death was not going to occur. It was thought at the start of the present investigation that intra-uterine death might be the result of a failure in placental circulation. If this were so it was hoped that the results of successive clearance tests would give some indication as to whether or not intra-uterine death was likely to occur. In other words it was hoped to find a critical level of myometrial blood flow below which the foetus was unlikely to survive. From the results obtained however it is apparent that the test does not lend itself to this sort of individual application because of the wide within patient variation. Furthermore in so far as it is a measure of placental circulation there is no evidence that any significant degree of placental circulatory failure occurs in the diabetic patient. It would appear that when intra-uterine death of the foetus does take place it is unrelated to the myometrial blood flow in the preceding weeks of the pregnancy. Indeed, taking the stillbirth, neonatal death and pulmonary syndrome group as a whole the mean clearance time was actually faster than when the infant survived.

The finding that mild pre-eclampsia complicating diabetes does not appear to affect the clearance time is surprising in view of the published reports on its effect on myometrial blood flow in non-diabetics (Morris *et al.*, 1955; Johnson and Clayton, 1957; Moore and Meyerscough, 1957). It does, however, confirm the impression that, using myometrial blood flow as an index of placental circulation, there is no evidence of a diminished placental blood flow in the pregnant diabetic even when the situation is further complicated by the presence of hydramnios. The effect of insulin dosage upon the clearance time is surprising for it is not clear why patients on high doses of insulin should have a faster mean clearance time than those on lower doses. The trend towards longer clearance times with increasing age might be expected from *a priori* considerations and has been confirmed by Moore and Meyerscough (1957). Nevertheless the majority of older patients had clearance times within the normal range and they do not show an increased foetal loss.

With the rejection of the idea of defective placental circulation as a cause of stillbirth and neonatal death in pregnancy complicated by diabetes one remains faced with the problem of an alternative explanation. At the present time clinical evidence strongly suggests that close clinical control is of paramount importance in reducing foetal loss, particularly intra-uterine death. The results of the present investigation support the idea that the high foetal survival rates obtained by such control are achieved independently of the maternal placental circulation which remains normal irrespective of the foetal outcome.

Summary and Conclusions

The myometrial blood flow in late pregnancy was estimated by the radioactive sodium clearance technique in 68 diabetic and 26 non-diabetic patients. In the diabetic patients the estimation was repeated on 2 or 3 occasions at fortnightly intervals.

No difference was demonstrated in the mean clearance times between the diabetic and non-diabetic groups. Mild pre-eclampsia did not adversely affect the clearance time in either group.

In the diabetic patients there was no increase in clearance time with increasing maturity, neither was there any correlation between the clearance time and hydramnios or maternal weight. The clearance time in those patients whose infants were stillborn, died in the neonatal period or recovered from the pulmonary syndrome, was faster than in the patients where the infant survived uneventfully. There was a similar correlation, implying increased myometrial/placental blood flow in the clearance times of those patients with a high dosage of insulin at the end of the pregnancy.

In spite of a wide variation between successive determinations in the same patient this was less than the variation between patients. The test was not found to be of any prognostic value in the individual diabetic patient as regards foetal outcome.

No evidence was found to support the idea that maternal placental blood flow is impaired in pregnant diabetics. The explanation for the increased foetal loss in this condition must therefore lie elsewhere.

Appendix

Investigations into Factors Affecting the Technique

After injection the background counting rate of the body rises due to the distribution of the ^{24}Na in the circulation away from the injection site. At the end of each test a reading was taken with the counter in the contralateral position to the site of injection. The rising body background counting rate was calculated from the formula:

$$c-b=c-\left(\frac{c(b_1-b_2)+Ib_2-b_1c_2}{I-c_2}\right)$$

where

- c is the observed counting rate over the injection site at any time, counts per minute.
- b is the required background counting rate at that time.
- b_1 is the initial background at the site of injection.
- b_2 is the final background at the identical contralateral position.
- c_2 is the observed counting rate at the injection site when $b=b_2$.
- I is the initial counting rate at the injection site, obtained by extrapolating the curve back to zero time.

This formula differs from Osborn's (Morris *et al.*, 1955) in that it allows the rising body background to be calculated even if all the injected material has not diffused away by the end of the test.

A Test for the Validity of this Background Correction

A similar G4Pb counter, with a rather wider angled collimation (Fig. 4B) than the original counter (Fig. 4A), was strapped on in the contralateral position to the injection site at the start of the test. The counter B readings should give a constant proportion of the rising body background as measured by the original counter A. The readings were recorded by a second ratemeter and pen-recorder, and plotted to give the rising body background.

In a series of 9 tests on 9 patients the mean clearance time using the rising background equation $=3{\cdot}41$ S.E. $\pm 0{\cdot}97$ minutes. The mean clearance time using the contralateral counter readings $=3{\cdot}64 \pm 0{\cdot}97$ minutes. Hence the equation used for calculating the rising body background seems to be valid.

Note of the Forms of the Plots After Subtraction of the Rising Background

After subtraction of the rising body background 118 of 183 plots gave a single straight line (Fig. 1a), from which the clearance time, $t\frac{1}{2}$, could be read directly. The remaining 65 plots were of the forms illustrated in Figure 1 b and c.

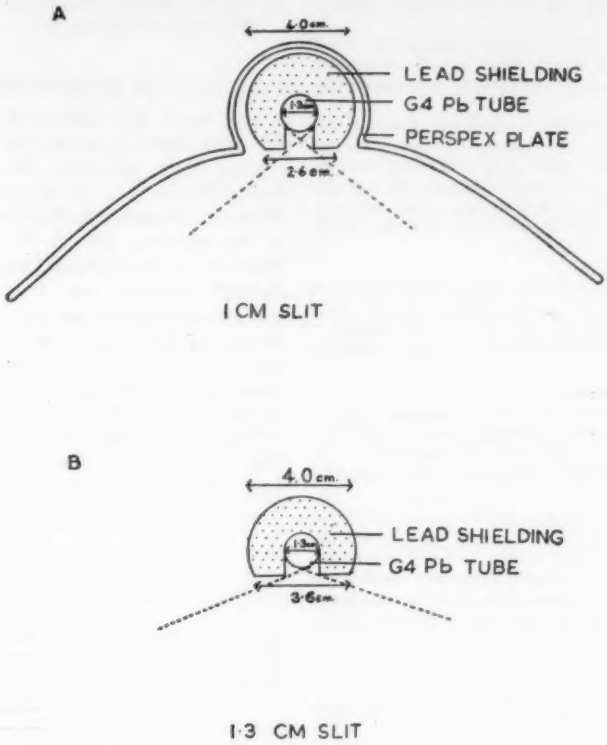

FIG. 4

Cross section of counters A and B showing the collimation.

Form (c) gave two components, $_1t_{\frac{1}{2}}$ and $_2t_{\frac{1}{2}}$, the second component obtained from the straight line portion of the curve was extrapolated back to zero time, and subtracted from the observed curve corrected for rising background. The differences were plotted to give a straight line for $_1t_{\frac{1}{2}}$.

A mathematical mean, the TOTAL CLEARANCE TIME (T.C.T.) was calculated from the values of $_1t_{\frac{1}{2}}$ and $_2t_{\frac{1}{2}}$ and the intercepts P+Q at zero time.

$$\text{T.C.T.} = {}_1t_{\frac{1}{2}}\left(\frac{Q}{P+Q}\right) + {}_2t_{\frac{1}{2}}\left(\frac{P}{P+Q}\right)$$

The mean value of T.C.T. for diabetics $= 3 \cdot 66 \pm 0 \cdot 27$ minutes.

The mean value of the clearance time for "1 component curves" $= 3 \cdot 59 \pm 0 \cdot 30$ minutes.

Form (b) cannot be analyzed in this way. A mean curve was drawn through the points. There were only 15 plots of this type.

Two component curves have not been reported by other workers.

An Attempt to Reduce the Number of Two Component Curves

It was suggested that the two component curves might be due to:

(*a*) Tracking back of the injection solution along the path of the needle, and subsequent removal by the skin capillaries since the second component was sometimes comparable with skin clearance times.

(*b*) The collimation of the counters limiting the field of view so that two mechanisms could be followed, a diffusion process and venous transport.

To test (*a*) in a series of 29 tests on 13 patients a small bubble of air was injected after the solution.

The mean clearance time "with bubble" $= 3 \cdot 66 \pm 0 \cdot 75$ minutes.

The mean clearance time for whole diabetic series = $3 \cdot 75 \pm 0 \cdot 28$ minutes.

The occurrence of two component curves was 36 ± 4 per cent in the whole diabetic series, and 31 ± 9 per cent in the "bubble" series. This fall is not statistically significant.

The bubble did not cause a significant change in the mean clearance time, or eradicate two component curves.

To test (*b*) (*i*) the wider angle collimated counter (Fig. 4B), and later (*ii*) a G4Pb shielded with 0·2 cm. thick lead, for $\frac{3}{4}$ of its circumference (C) were mounted alongside the original counter, and readings taken simultaneously.

(*i*) 4 tests on 4 patients:

Wider angled collimation (Fig. 4B), mean clearance time = $3 \cdot 18 \pm 0 \cdot 87$ minutes original counter (Fig. 4A), mean clearance time = $2 \cdot 53 \pm 0 \cdot 46$ minutes.

There is no significant difference in these clearance times.

(*ii*) 21 tests on 9 patients:

Shielded counter (C), mean clearance time = $2 \cdot 87 \pm 0 \cdot 40$ minutes original counter (Fig. 4A), mean clearance time = $3 \cdot 64 \pm 0 \cdot 86$ minutes.

There is no significant difference in these clearance times.

The overall occurrence of 2 component curves in the less collimated counters B and C = 36 ± 9 per cent and for those tests with the original counter A, = 40 ± 10 per cent.

It appears that the collimation does not significantly alter the mean clearance times. The fall in the occurrence of 2 component curves by 4 per cent is not statistically significant.

Conclusions

(1) The rising background equation used seems quite valid.

(2) The two component curves do not appear to be due to a skin clearance and the uterine clearance rate being observed simultaneously.

(3) The two component curves are not a function of the collimation of the counter.

Acknowledgments

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CYSTS OF THE VAGINAL WALL

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ALTHOUGH vaginal wall cysts are relatively common there is still much divergence of opinion concerning their pathological classification. A source of difficulty is the apparent absence of a specific histological pattern corresponding to each type of cyst. Indeed so many different types of lining have been ascribed to the mesonephric (Gärtner's) duct cyst (Novak, 1958) that there are few vaginal cysts which cannot, on such a histological basis, be included under this heading. As Blackwell and McElin (1955) remark, "the diagnosis of terminal mesonephric duct cysis is predominantly a clinical diagnosis". Cysts so diagnosed are liable to retain their label whatever their histology. This may well contribute to the polymorphic lining ascribed to the mesonephric duct cyst.

We have searched the literature in an attempt to find a rational basis for the identification of vaginal cysts, and have evolved a method which enables the origin of most vaginal cysts to be defined. This method has been used to analyze forty-two consecutive cases of vaginal wall cyst.

HISTORICAL SURVEY

Heming (1831) considered that most vaginal cysts originated from obstructed lacunae or pits in the vaginal wall. Occasionally he was able to trace "a continuation of the mucous membrane of the vagina into the tumour". Huguier (1847) divided vaginal cysts into superficial and deep, and noted a relationship to pregnancy.

Von Winckel (1887) also divided vaginal cysts into superficial and deep; the superficial arising from vaginal glands and, rarely, from dilated lymph sinuses or trauma; the deep-seated, having a muscular wall, arising from mesonephric (Gärtner's or Wolffian) ducts or un-united paramesonephric (Müllerian) duct rudiments. The latter had been described by Freund (1877) as a variant of the double genital canal, with one paramesonephric duct forming the whole vagina, the other remaining rudimentary and later becoming cystic. Winckel also drew attention to the occasional occurrence of multiple small gas cysts of the vaginal wall, possibly arising in vaginal glands.

The existence of vaginal glands has been much disputed. Von Preuschen (1877) after a careful examination of thirty-six bodies demonstrated vaginal glands in four. His drawings show glands having necks lined by stratified squamous epithelium and a deeper portion lined by a single layer of columnar ciliated epithelium. Johnston (1887) quotes twenty authors who confirm the presence of glands in the vagina and a similar number who doubt or deny their existence. Plaut and Dreyfuss (1940), also Studdiford (1957), describe adenosis of the vagina, characterized by glands or cysts lined by tall columnar mucus-secreting cells with basal nuclei resembling those lining the cervical glands. Novak (1958) concludes that glands are not normally present in the vagina, though rarely a few glands may be found in the fornix,

usually aberrant cervical glands or gland-like tubules derived from the vestigial mesonephric duct.

The suggestion that certain vaginal cysts arose from the mesonephric ducts was made by Veit (1867). Reider (1884) examined 40 female bodies and found mesonephric ducts complete with epithelial lining in one-fifth of the cases and without epithelial lining in one-sixth. Cullen (1905) considered that 11 out of his series of 53 vaginal cysts were probably derived from mesonephric ducts. He described the mesonephric duct as having "an inner lining of one layer of cuboidal or cylindrical epithelium", and its cysts as having a similar lining, sometimes more flattened. The histological identity of the mesonephric duct throughout its length is supported by the work of Buerger and Petzing (1954) on mesonephric duct cysts in the wall of the uterus, and of Gardner, Greene and Peckham (1948) on mesonephric duct cysts of the broad ligament.

The mesonephric duct is typically non-ciliated, but ciliated epithelium has occasionally been described in mesonephric duct cysts (Strong, 1920; Blackwell and McElin, 1955; Novak, 1958). The presence of cilia was considered by Hartmann (1919) to indicate a paramesonephric duct origin. This is not necessarily inconsistent, for many types of epithelium which are typically non-ciliated may on occasions develop cilia (Willis, 1960).

Implantation or epidermoid cysts of the vagina were already well recognized by the time of Cullen (1905). He gave a clear description of their situation in the posterior or lower lateral vaginal wall, often in the scar tissue of an old tear, and of their histological structure with stratified squamous lining, sometimes associated with giant cells. Unlike the other cysts described above implantation cysts of the vagina do not appear to have caused difficulty in identification.

Present Study

Material

All vaginal cysts sent for pathological examination at the Jessop Hospital for Women, Sheffield, from January, 1950 to September, 1956, have been included in the present series of 42 cases. Twenty-two had been excised as isolated surgical procedures or with some other minor procedure and the remainder were removed at the time of a major operation. The routine histological preparations were in most cases quite satisfactory for our present study. In a few instances fresh sections were cut from the paraffin blocks. Staining was by Ehrlich's haematoxylin and alcoholic eosin and in some instances Mayer's mucicarmine and Masson's trichrome.

Method

The cyst wall was first examined histologically, without knowledge of the associated clinical condition or the previous pathological report. Histological diagnosis was made on the criteria discussed below. It was then assessed in the light of the anatomical situation of the cyst, the clinical history and the previous pathological report.

Basis of Present Classification

The formation of vaginal cysts is closely related to the embryological development and anatomy of the vagina.

Embryology

There is general agreement on the development of the Fallopian tubes, uterus, cervix and upper vagina by a caudal growth of the paramesonephric ducts, partial mid-line fusion, and subsequent canalization. It is also generally accepted that remnants of the mesonephric ducts persist along a line extending from the broad ligament, lateral to or through the muscle of the uterus and cervix, antero-laterally in the tissues of the vaginal wall, and ending anteriorly in the labia. There is however much controversy about the embryology of the hymen and lower third of the vagina. Where the fused paramesonephric ducts meet urogenital sinus there is a tendency for the epithelial cells of urogenital sinus origin to proliferate and merge with or replace the cells of the fused paramesonephric ducts. Some authors believe that the hymen arises from Müller's tubercle, and is lined internally by vaginal epithelium and externally by urogenital sinus epithelium

(Bloomfield and Frazer, 1927). Others believe that the lower third of the vagina and the hymen are derived from the urogenital sinus (Koff, 1933).

Anatomy

The structures whose close relationship to the vagina must be remembered in considering vaginal cysts, are the urethra, with the para-urethral glands, the bladder and mesonephric (Gärtner's) ducts anteriorly; the rectum and pouch of Douglas posteriorly, with the intervening recto-vaginal septum; an aberrant ureter laterally; and the vestibular glands inferiorly.

Histology

I. Cysts of Mesonephric (Gärtner's or Wolffian) Duct Origin

Mesonephric duct cysts in the broad ligament and lateral wall of the uterus are lined by a single layer of non-ciliated, non-secretory cubical epithelium composed of small regular cells on a well-defined basement membrane, usually surrounded by a wall of smooth muscle (Gardner *et al.*, 1948; Buerger and Petzing, 1954). We consider the same histological features to be characteristic of mesonephric duct cysts in the vaginal wall (Figs. 1 and 2). Patches of squamous metaplasia are fairly common. The presence of cilia is atypical but may occasionally occur. Evidence of secretory activity is against a mesonephric duct origin.

II. Cysts of Paramesonephric (Müllerian) Duct Origin

The paramesonephric ducts give rise to the Fallopian tubes, endometrium, cervix and most of the vagina. Vaginal wall cysts may be seen showing a histological structure corresponding to each of these four tissue types. The term paramesonephric duct cyst is however often used with particular reference to cysts having a lining of cervical or Fallopian tube type. These will be considered first.

(1) The cervical type of cyst is characteristically lined by tall columnar cells with basal nuclei, often called "picket" cells (Fig. 3), frequently showing abundant mucin secretion with the formation of retention cysts resembling the Nabothian cysts of the cervix. The cells lining the main retention cyst may be flattened by the presence of the contents or undergo squamous metaplasia (see Fig. 4) so that the typical "picket" cells may have to be searched for in microscopic cysts adjoining the main cyst cavity (see Fig. 5). Sometimes papillary processes are present (Fig. 6) resembling a papillary endocervicitis. These cysts appear to be identical with those described by Plaut and Dreyfuss (1940) and Studdiford (1957) under the heading of adenosis of the vagina.

(2) The Fallopian tube type of paramesonephric duct cyst is lined by a rather irregular columnar epithelium, partly ciliated, partly secretory (Figs. 7 and 8) with poorly defined basement membrane, as in the paramesonephric duct cysts of the broad ligament described by Gardner *et al.* (1948).

Sometimes both Fallopian tube and cervical types of lining may be found in the same cyst. It is therefore convenient to group them together under the heading of paramesonephric duct cysts of "mucous" type.

(3) The endometriotic cyst, being derived from endometrial tissue, is also of paramesonephric duct origin. It is usually readily recognized by the presence of endometrial glands and stroma (Fig. 9). On one occasion a careful search revealed columnar ciliated epithelium, a variant which we have also seen in the endometrium itself. Sometimes the histological appearance is obscured by haemorrhage, usually with collections of macrophages containing haemosiderin. In such cases the presence of endometriosis elsewhere is useful circumstantial evidence.

(4) The epidermoid or implantation cyst, usually situated on the posterior vaginal wall at the site of previous trauma, appears to have the same structure whether derived from the upper (paramesonephric duct) or lower (urogenital sinus) portion of the vagina. It is lined by stratified squamous epithelium (Fig. 10), often with an associated foreign body giant cell reaction.

In none of the present series did a cyst appear to have originated from failure of fusion of the paramesonephric (Müllerian) ducts as a variant

Table Summarizing Differential Characteristics of Common Vaginal Cysts

Epithelial Lining	Basement Membrane	Surrounding Tissue	Other Features
		I.—Mesonephric Duct Cysts	
Non-secretory epithelium, typically non-ciliated, usually low columnar but it may be flattened. Mucicarmine negative. Tendency to squamous metaplasia.	Well defined basement membrane.	Surrounding unstriated muscle coat often present.	Almost always in anterior vaginal wall, usually antero-lateral.
		II.—Paramesonephric Duct Cysts (Mucous)	
Epithelium resembling lining of endocervix or Fallopian tube. Mucicarmine positive. (*i*) Endocervical type. Tall mucus-secreting columnar cells with basal nuclei ("picket cells"), best seen in smaller subsidiary cysts. Cells often flattened in main cyst by pressure of contents (mucinous fluid). (*ii*) Fallopian tube type. Columnar cells of varying size, some ciliated and some mucus-secreting.	Poorly defined basement membrane.	Absence of endometrial type stroma (cf. endometriosis).	Usually solitary. Multiple small scattered cysts may be present.
		III.—Endometriotic Cysts	
Columnar epithelium resembling endometrial glands and sometimes showing corresponding cyclical changes. Distortion and destruction of the epithelium by haemorrhage is often present.	Fairly well defined basement membrane.	Endometrial type stroma surrounding the typical epithelium is diagnostic. Macrophages containing haemosiderin may be numerous.	There may be evidence of endometriosis elsewhere.
		IV.—Epidermoid or Implantation Cysts	
Stratified squamous epithelium.	Poorly defined basement membrane.	Foreign body giant cell reaction may be present.	Usually situated in posterior vaginal wall at site of previous trauma.

of the double genital canal described by Freund (1877), for which the term Müllerian duct cyst of the vagina was originally used. There is however no reason to doubt the existence of such cysts.

III. Rare Types of Vaginal Cyst

Only three cysts in our series did not fall into the categories described above. One was a diverticulum of the bladder, lined by transitional epithelium (Fig. 11) whose removal was followed by a vesico-vaginal fistula. Another was a Bartholin's cyst which had evidently been displaced from its normal site by a previous plastic repair and histologically showed compound racemose mucous glands adjoining the lining transitional epithelium.

The third was an example of vaginitis emphysematosa. The cysts, which *in vivo* contained gas, are thin-walled (Fig. 12) and in places the lining cells can be identified as flattened multinucleate giant cells (Fig. 13), as described by Bender and Jeffcoate (1950). In several of the cysts no distinct lining cells can be detected. The adjacent connective tissue shows leucocytic infiltration.

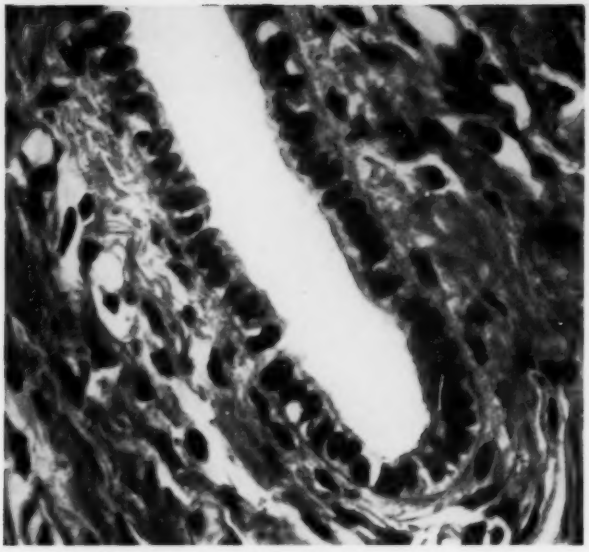

FIG. 1

Mesonephric duct cyst lined by small cubical cells, regularly aligned on a definite basement membrane. ×800.

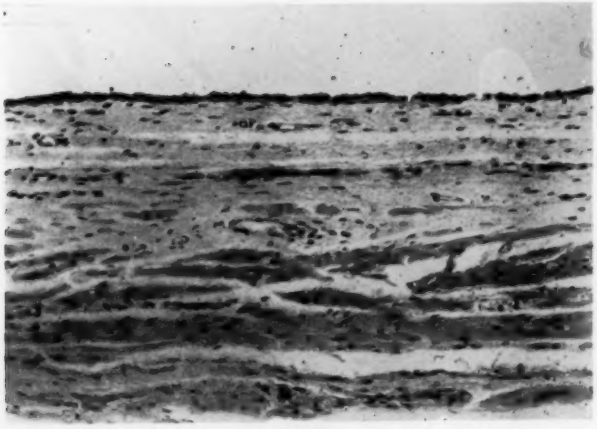

FIG. 2

Mesonephric duct cyst, showing unstriated muscle coat in wall of cyst. ×160.

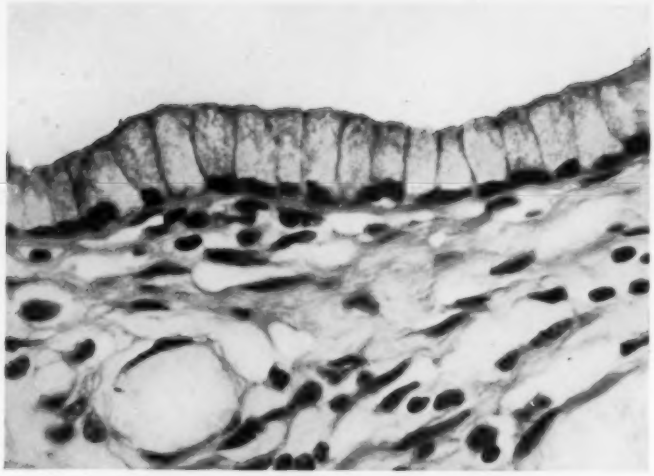

FIG. 3

Paramesonephric duct cyst of cervical type. The tall columnar cells with basal nuclei, from a subsidiary cyst of section shown in Figure 4, resemble endocervical "picket" cells. ×710.

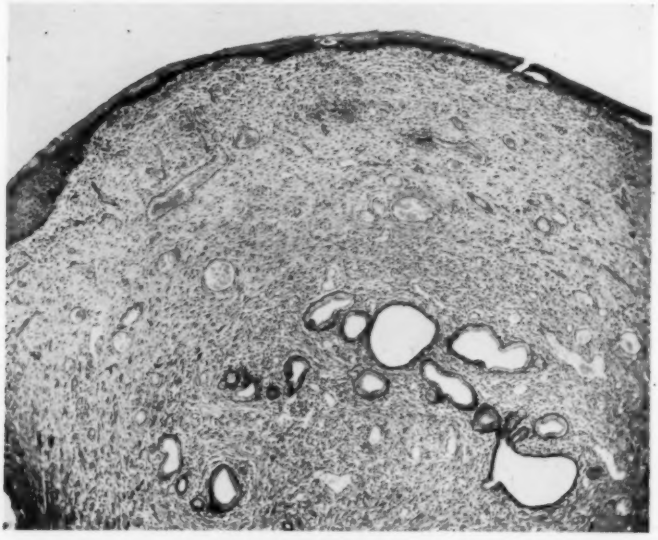

FIG. 4

Paramesonephric duct cyst of cervical type. Stratified squamous epithelium lines the main cyst cavity. ×28.

FIG. 5

Subsidiary cysts from section shown in Figure 4, illustrating close resemblance to endocervical tissue. ×235.

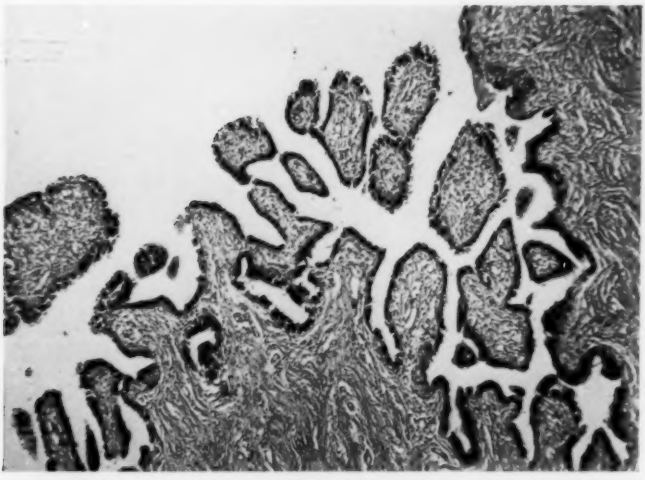

FIG. 6

Paramesonephric duct cyst of cervical type. The lining is raised into papillary processes, resembling papillary cervical erosion. ×70.

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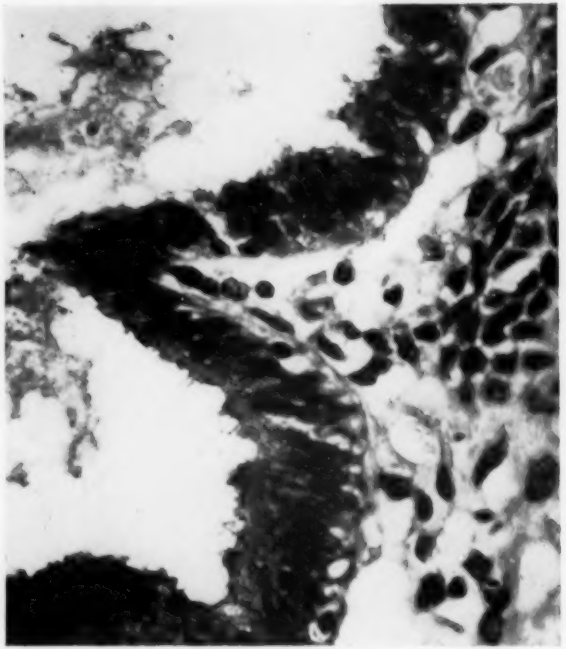

FIG. 7

Paramesonephric duct cyst of Fallopian tube type, lined by uneven columnar ciliated and mucus-secreting cells. ×695.

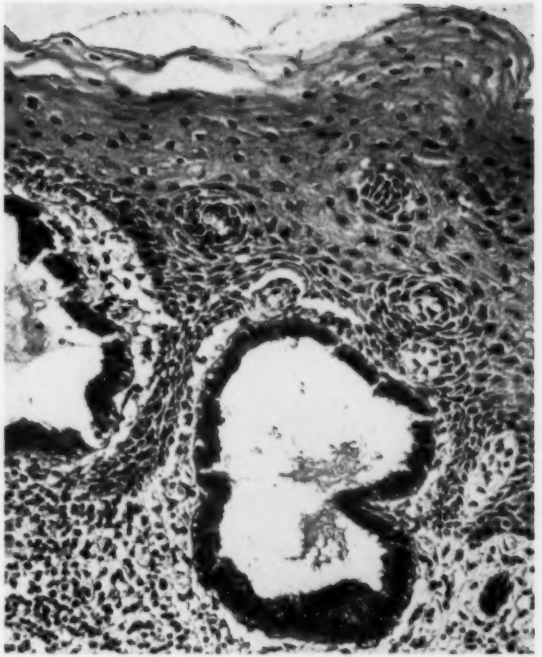

FIG. 8

Same section as Figure 6, showing superficial situation of cysts in vaginal wall. The cysts are surrounded by chronic inflammatory cells. ×180.

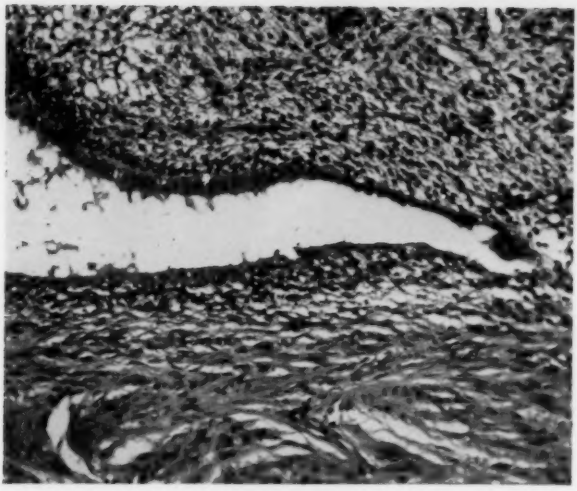

FIG. 9

Endometriotic cyst, with lining resembling endometrial glands and stroma. ×143.

FIG. 10

Epidermoid or implantation cyst, lined by stratified squamous epithelium with squames desquamating into the cyst cavity. Slight inflammatory exudate is present. ×131.

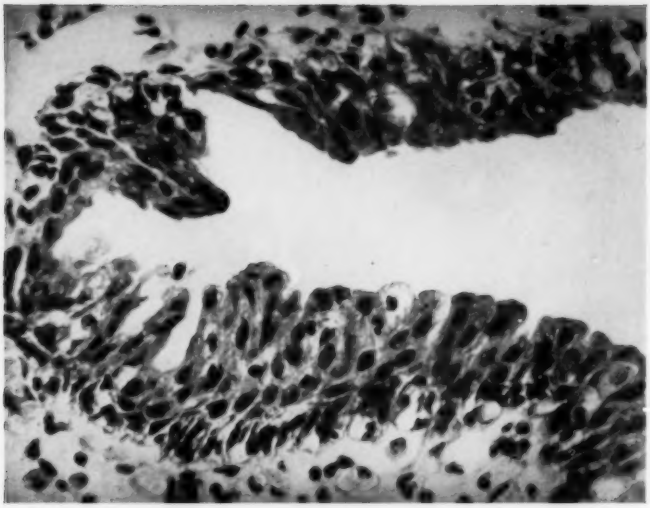

FIG. 11

Bladder diverticulum, lined by transitional epithelium of urinary tract type, with slight inflammatory infiltration. ×490.

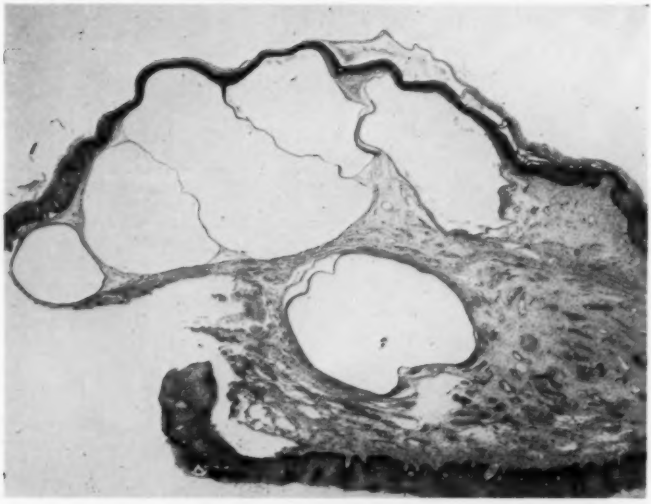

FIG. 12

Vaginitis emphysematosa. The cysts, which contained gas *in vivo*, are superficially situated and very thin-walled. ×17.

FIG. 13

Same case as Figure 12, showing a multinucleate lining cell whose structure is consistent with a flattened giant cell. ×425.

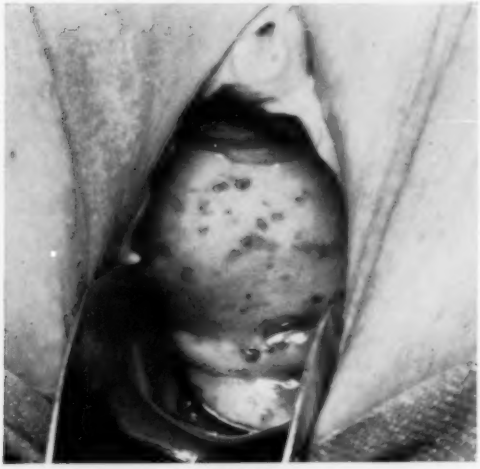

FIG. 14

Multiple small cysts of vaginal wall. These became evident after treatment of monilial vaginitis with gentian violet. The histology is shown in Figures 7 and 8.

Results

Of the 42 cysts, 30 were considered to be of paramesonephric duct origin and 9 of mesonephric duct origin, with one bladder diverticulum, one displaced Bartholin's cyst and one vaginitis emphysematosa. Of the 30 cysts of paramesonephric duct origin, 15 were of cervical type, 5 were of Fallopian tube type, 6 were endometriotic cysts and 4 were epidermoid inclusions.

The majority of cysts in the vaginal wall were thus found to be of paramesonephric duct origin. These were more than three times as common as those of mesonephric duct origin.

Anatomical Correlation

The mesonephric duct cysts, with one exception, were situated in the anterior vaginal wall. (The exception was pedunculated and probably displaced from its original position.) But only 8 of the 16 anterior wall cysts were found to be of mesonephric duct origin. The other 8 comprised one bladder diverticulum and 7 paramesonephric duct cysts, of which 4 were of cervical type and 3 of Fallopian tube type. It is clear that an anterior wall situation by no means implies a mesonephric duct origin.

The epidermoid (implantation) cysts were situated in all 4 cases in the posterior wall at the site of previous trauma. The remaining paramesonephric duct cysts showed little anatomical constancy apart from those of cervical type which were slightly commoner near the fornices. The endometriotic cysts were variable in situation but in several cases were associated with endometriosis elsewhere.

The paramesonephric duct cysts of cervical and Fallopian tube type formed a group of 20 cases which may conveniently be considered together. These cysts were superficially situated and contained mucus. They were usually solitary but in 3 cases were multiple (Fig. 14). They so closely resembled the "vaginal gland" cysts of the 19th century writers that we carried out an extensive search for glands in vaginal wall tissue from post-mortem and operation (pelvic repair) material. Our findings were negative, apart from very occasional ectopic cervical glands in the fornices.

In the case of vaginitis emphysematosa, multiple superficial bullae were present on the upper two-thirds of both anterior and posterior vaginal walls, occurring during pregnancy. On puncturing these bullae with a fine needle, gas was heard to escape with a hiss.

Clinical Importance

The chief clinical significance of vaginal wall cysts is the danger of obstruction to labour by a large cyst. Increase in size may be very rapid during pregnancy. An occasional effect of vaginal wall cysts is dyspareunia, less commonly dysuria, and occasionally prolapse.

The importance of the bladder diverticulum needs to be stressed out of all proportion to its relative incidence. If mistakenly excised as a vaginal cyst, the resultant disability from vesicovaginal fistula is so great that the possibility must always be excluded, if necessary by cystoscopy or radiography.

There were 20 cases of paramesonephric duct cysts of "mucous" type (i.e., showing a structure resembling cervix or Fallopian tube). In the majority of these the cysts were solitary with practically no symptoms. In 3 cases, however, which presented with vaginal discharge or bleeding, the vaginal walls were studded with small cysts, in one case becoming evident after treatment of a monilial vaginitis with gentian violet (see Fig. 14). As previously mentioned, these are evidently examples of the lesions described by Plaut and Dreyfuss (1940) as adenosis of the vagina.

Discussion

Mesonephric duct cysts are situated in the anterior vaginal wall. The apparent corollary that anterior vaginal wall cysts are mesonephric is a familar type of logical fallacy. Only half the anterior wall cysts were found to be mesonephric in the present series, forming less than a quarter of the total number. The diagnosis of cysts as "mesonephric" on the basis of their anterior wall situation may account for some of the confusion to be found in the literature on vaginal cysts. It would also make mesonephric duct cysts appear disproportionately common.

Thirty out of the forty-two cases in the present series were found to be of paramesonephric duct origin. If we exclude from this group the 6 endometriotic cysts and the 4 epidermoid cysts, there remains a group of 20 paramesonephric duct cysts of "mucous" type, i.e., having a histological structure resembling cervix or Fallopian tube with the appropriate mucus-secreting cells. Cysts of this group are so similar to the "vaginal gland" cysts of earlier writers, e.g., the superficial cysts of Huguier (1847) and Winckel (1887), that it seems very likely that they are the same entities, differently interpreted. They also correspond to the lesions described by Plaut and Dreyfuss (1940) and Studdiford (1957) as adenosis of the vagina. In Cullen's series (1905) only 4 out of the 53 cases were of this type. Their higher incidence in the present series may be related to their relative absence of symptoms and the more readily obtained medical attention under the National Health Service.

The vagina is mainly derived from paramesonephric duct tissue, which is of mesenchymal origin. Tissues of mesenchymal origin have a remarkable capacity for metaplasia, even in adults, not infrequently regaining their embryonic pluripotency in the course of regeneration (Willis, 1953). This characteristic may account for the relatively high incidence of vaginal cysts whose histological structure suggests localized heterotopic paramesonephric differentiation.

The commonest cyst in Cullen's series was the traumatic or epidermoid cyst, comprising 26 out of his 53 cases. In our series only 4 were of this type. The histological characteristics were already too well defined in 1905 for this discrepancy to be due to difference in interpretation. A possible explanation is that over the last fifty years improvements in midwifery practice may have led to reduced vaginal trauma and more accurate perineal repair.

Summary

(1) A series of 42 consecutive cases of vaginal wall cysts is presented.

(2) An attempt has been made to clarify the features by which the various types of cyst may be identified. These are summarized in the accompanying table.

(3) Vaginal wall cysts may be broadly divided into those of paramesonephric and those of mesonephric duct origin.

(4) Cysts of paramesonephric duct origin may be subdivided into (*a*) "mucous" cysts of cervical and Fallopian tube types, (*b*) endometriotic cysts and (*c*) epidermoid (implantation) cysts.

(5) The majority of cysts in the present series were found to be of paramesonephric duct origin, mainly of "mucous" type.

(6) Mesonephric duct cysts accounted for less than a quarter of the total number, and approximately a half of the anterior wall cysts.

(7) The danger of a bladder diverticulum presenting as an anterior vaginal wall cyst is mentioned.

We wish to thank Mr. D. H. Lees, Mr. L. B. Patrick and Professor C. S. Russell for access to the case records, Dr. C. G. Paine and Professor R. A. Willis for their kind encouragement and advice, and also Mr. R. Marshall and Mr. J. G. Haddock for their assistance with the photomicrography.

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MEGALOBLASTIC ANAEMIA OF PREGNANCY AND THE PUERPERIUM

BY

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MEGALOBLASTIC anaemia is no longer regarded as an uncommon complication of childbearing. Forshaw (1958) from Liverpool, reports an incidence of 1 case in every 67 confinements and, in a previous paper, Forshaw *et al.* (1957) gave an incidence of 1 in 190 confinements. At Stoke-on-Trent, Giles and Shuttleworth (1958) found 1 case in every 39 confinements. Each of these authors discusses the haematological, clinical and aetiological features of the disease.

The present paper records the incidence of megaloblastic anaemia of pregnancy in an industrial area in the West Riding of Yorkshire. St. Luke's Maternity Hospital, Bradford, serves a population of approximately 350,000. Between 1st January, 1955 and 31st December, 1958, 116 cases of megaloblastic anaemia of pregnancy were diagnosed. About one-half of these were studied personally, details of the others were obtained from the records. An account of the clinical, haematological and aetiological features of these cases is now given.

METHOD

Routine haemoglobin estimations are performed on every antenatal patient at the first attendance and at the 30th week of pregnancy. Further estimations are carried out if indicated. When the haemoglobin is 10 g. or less a film is examined (100 per cent=14·8 g.). "Buffy coat" preparations were made as described by Goodall (1957). The bone marrow was examined by iliac crest puncture. Red cell counts and absolute values are not done routinely. The diagnostic criterion was the presence of megaloblasts in blood or "buffy coat" films or in the marrow aspirate.

The control series was obtained by recording the relevant details of every fiftieth patient on the maternity register during the calendar years 1955–58. In this way data from 210 patients, none of whom had megaloblastic anaemia, were obtained.

INCIDENCE

One hundred and sixteen cases were diagnosed during the 4 years mentioned and there were 10,629 confinements. This makes the overall incidence of megaloblastic anaemia at this hospital 1 in every 92 confinements. The incidence in each of the 4 years is shown in Table I.

LABORATORY FINDINGS

Method of Diagnosis

In 44 patients megaloblasts were found in the routine blood film. In a further 11 patients megaloblasts were present in "buffy coat" preparations. The remaining 61 patients required bone marrow aspiration to establish the diagnosis.

TABLE I

Yearly Incidence of Megaloblastic Anaemia

Year	1955	1956	1957	1958
Number of confinements	2,421	2,629	2,734	2,845
Number of cases	25	20	31	40
Incidence	1 in 97	1 in 131	1 in 88	1 in 71

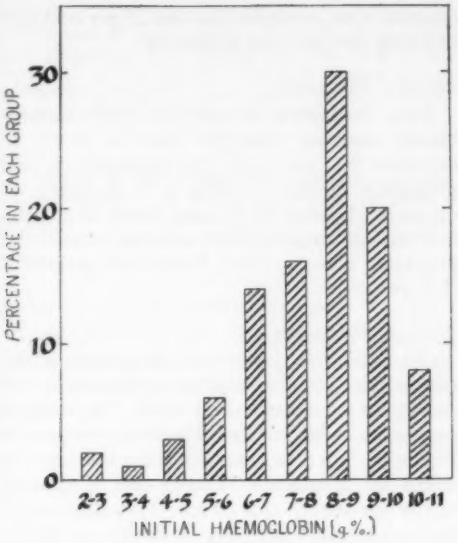

FIG. 1
Degree of anaemia.

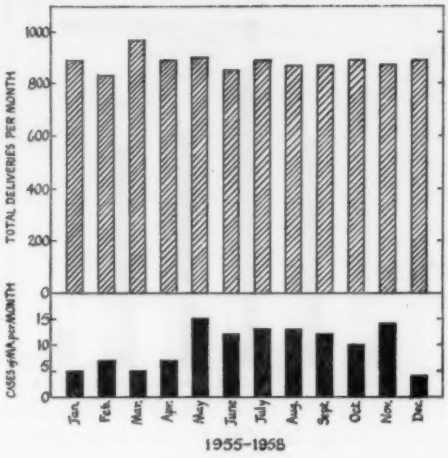

FIG. 2
Seasonal incidence.

Degree of Anaemia

The haemoglobin levels at the time of diagnosis are shown in Figure 1. These range between 2·5 and 10·9 g., the mean being 8 g.

Peripheral Blood Picture

Ninety patients showed macrocytosis. In 71 there was hypochromia indicating concurrent iron deficiency. Megaloblastic anaemia only became manifest in 11 of these patients after administration of iron.

Gastric Secretion

Histamine test meals were done on 10 patients and 2, aged 39 and 43 years respectively, had achlorhydria. It must be remembered, however, that gastric acidity is often reduced during pregnancy (Murray *et al.*, 1957).

Response to Treatment

All patients were given 20 mg. of folic acid daily. Twenty-seven also received 100 to 400 μg. of vitamin B_{12} per week. Oral or parenteral iron was also given to correct concurrent iron deficiency. Details of the results were available for 76 patients. In each, the reticulocyte count and haemoglobin levels indicated a satisfactory response. The addition of vitamin B_{12} did not appear to make any difference to the response. Seventeen patients received a blood transfusion. In 7 the indication was ante- or post-partum haemorrhage. One was given fresh blood on account of thrombocytopenia. The other 9 were transfused to correct anaemia. The average haemoglobin level at that time was 6·9 g.

CLINICAL FEATURES

Seasonal Incidence

The highest incidence of megaloblastic anaemia is during the period from May to November (Fig. 2). This is not due to any variation in the total number of confinements which differs very little from month to month.

Age Incidence

The age incidence is shown in Figure 3 along with that of the control series. The average age

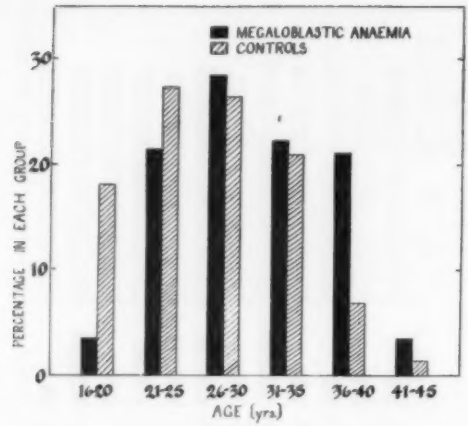

FIG. 3
Age distribution.

was 29·9 years, and that of the controls 26·8 years. Only 3·6 per cent of patients were under 20 years compared with 18·1 per cent of the controls.

Parity

Just over 10 per cent of patients were primigravidae and nearly 60 per cent of cases occurred during the second, third or fourth pregnancy (Fig. 4). In contrast, about 40 per cent of the controls were primigravidae and 25 per cent had had only one previous pregnancy.

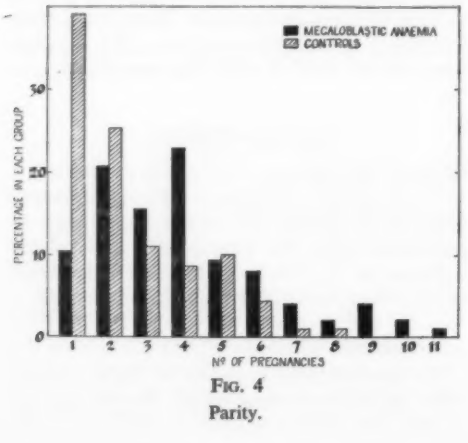

FIG. 4
Parity.

Multiple Pregnancy

Twin pregnancy in patients with megaloblastic anaemia occurred once in every 12 deliveries (8·3 per cent). The incidence of twin pregnancy at this hospital is 1 in every 42 deliveries. During the 4 years under study, the incidence of megaloblastic anaemia in multiple pregnancy was 1 in every 26 multiple gestations (3·8 per cent).

Stage of Pregnancy

One-half of the cases were diagnosed in the puerperium, 53 during the first week and the rest during the second and third weeks. The stage of pregnancy at the time of diagnosis is shown in Figure 5. The majority occur in the last six weeks of pregnancy. Three were diagnosed before the twenty-ninth week. They all showed unusual features and brief histories are given.

Case A

Diagnosed at the sixteenth week. Aged 43 years and third pregnancy. She had mitral stenosis. There was a poor response to parenteral iron and megaloblastic anaemia was diagnosed, the haemoglobin being 8·9 g. Achlorhydria was present. She responded to treatment, but failed to report after discharge. She may have been developing pernicious anaemia as she was over forty.

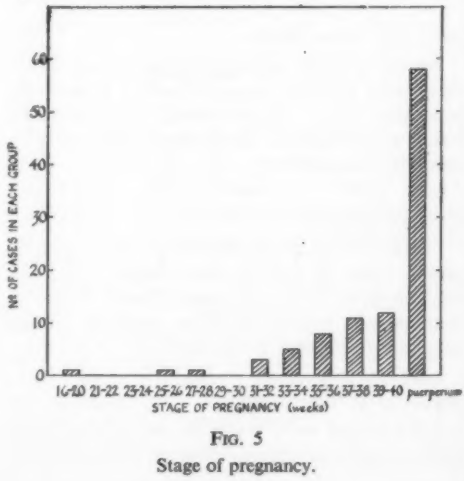

FIG. 5
Stage of pregnancy.

Case B

Diagnosed at twenty-sixth week. Aged 40 years and sixth pregnancy. The haemoglobin was 10·9 g. She responded to treatment but died after delivery from a carcinoma of the lung. Megaloblastic anaemia is sometimes associated with malignant disease.

Case C

Diagnosed at twenty-eighth week. Aged 29 years and fourth pregnancy. She was a strict Hindu. The haemoglobin was 7·4 g. There was a good response to treatment. Defective diet was probably an important factor in this case.

Recurrence of Megaloblastic Anaemia

Eight patients had megaloblastic anaemia during a previous or subsequent pregnancy and in one instance it appeared in three successive pregnancies. Two other patients developed macrocytic anaemia during a subsequent pregnancy, but no megaloblasts were found.

Family History

The mother of one patient suffered from pernicious anaemia.

Race

Seven patients were Indians or Pakistanis and four of these were strict Hindus. The remaining 109 patients were Europeans of British or Polish extraction.

Anti-convulsant Drugs

Two patients gave a history of epilepsy, but had not been taking anti-convulsant drugs for some time.

Blood Groups

A study of a collective series from a number of centres, of ABO blood-group distribution in pernicious anaemia reported by Aird *et al.* (1956) showed an increased incidence of Group A. The distribution of the ABO groups in 89 of the present series of patients is compared with that of the controls in Table II. The findings for 100 cases reported by Giles and Shuttleworth (1959) are also tabulated. There appears to be a small increase in the frequency of Group A in megaloblastic anaemia of pregnancy, but the total number of cases is still too small to permit a definite conclusion.

TABLE II

Blood-Group Distribution

(Percentage figures)

Blood Group	Present Series		Giles and Shuttleworth (1959)	
	Patients (89)	Controls (210)	Patients (100)	Controls (1,000)
O ..	45	49	42	45·6
A ..	46	40	51	42·9
B ..	7	8	5	8·3
AB ..	2	3	2	3·2

Antenatal Care

Thirty-six per cent of all patients with megaloblastic anaemia had received very inadequate antenatal care, either through infrequent attendance at the clinic or failure to make arrangements during pregnancy. In contrast, only 14 per cent of the controls had received inadequate antenatal care.

Occupation and Social Status

Twenty per cent of patients had worked during the pregnancy which was complicated by megaloblastic anaemia. Thirty per cent of controls worked during pregnancy. The lower incidence in the megaloblastic series is probably because more of these patients are multiparae who cannot work on account of young families (Giles and Shuttleworth, 1958). Information was available about the husbands of 87 patients. Eighty-one were working, 1 was unemployed, 1 was in prison and 3 were deceased. One patient was unmarried. Table III shows that the majority of patients belong to the Registrar General's social classes III, IV, and V, 69 per cent being

TABLE III

Distribution According to Registrar General's Social Classes

Class	Patients (19)	Husbands (81)	%
I	0	0	0
II ..	0	4	4
III ..	16	53	69
IV ..	2	10	12
V	1	14	15

in class III (craftsmen and other skilled workers). Only 4 per cent were in class II.

Complications

There was one maternal death (0·9 per cent) due to carcinoma of the lung. The perinatal mortality differed very little from that of the controls. Five infants were stillborn and another died after operation for oesophageal atresia. The various obstetric complications are shown in Table IV. The incidence of infection is nearly twice as high as in the control series. There is little difference in the total incidence of haemorrhage between the two groups, but ante-partum haemorrhage occurs more often in the megaloblastic anaemia series. The incidence of hypertension and albuminuria was less than that of the controls.

Discussion

The overall incidence of megaloblastic anaemia of pregnancy and the puerperium in Bradford is lower than that reported from other centres (Forshaw, 1958; Giles and Shuttleworth, 1958). However, during the last of the 4 years under study, the incidence was 1 in every 71 deliveries which is close to that reported by Forshaw (1958).

The seasonal variation shown by the present series (Fig. 3), differs from that reported by Thompson (1957) who found the highest incidence during the winter and spring months. He suggests that this variation may be due to a dietary deficiency of fresh green vegetables which are scarce during the winter months. It is difficult to reconcile this suggestion with the high incidence during the summer and autumn in the present series. Giles and Shuttleworth (1958) found no significant seasonal variation.

The peripheral blood picture is very variable in megaloblastic anaemia of pregnancy and the appearance of the red cells is not characteristic. Macrocytosis is not always present and hypochromia may dominate the picture. The diagnosis can only be made by demonstrating the presence of megaloblasts. The occurrence of megaloblasts in the peripheral blood has been regarded as uncommon (Davis and Brown, 1953; Giles and Shuttleworth, 1958). It will be recalled that, in 44 of the present 116 cases, megaloblasts were found in the routine blood film and, in 11 others, "buffy coat" films revealed them. Thus nearly half of the patients were spared the discomfort of marrow aspiration.

The anaemia is not always severe. Only a quarter of the patients in the present series presented with haemoglobin levels under 7·0 g. and the majority were 8 g. or more (Fig. 1). The belief that the anaemia is always severe and that megaloblasts are rarely found in the peripheral blood may help to explain why so few cases were detected until recent years.

Iron deficiency is often associated with megaloblastic anaemia of pregnancy. It was present in 71 patients from the present series. The appearance of megaloblastic anaemia after correction of iron deficiency is a characteristic but not very common mode of presentation.

Oral folic acid appears to be the treatment of choice. However, it may be advisable to give vitamin B_{12} to older patients to avoid precipitating neurological complications. Blood transfusion should not often be required in the routine treatment of megaloblastic anaemia. It is indicated if ante-partum or post-partum haemorrhage occurs and is perhaps permissible in patients diagnosed near term with a very low haemoglobin level. It is hardly justifiable to expose patients with megaloblastic anaemia to the risks associated with transfusion in order to hasten their discharge after an uncomplicated delivery.

Table IV

The Incidence of Complications in Patients with Megaloblastic Anaemia Compared with the Control Series

Complication	Megaloblastic (%)	Controls (%)
Infection of birth passages ..	6·9	3·8
Breast abscess	2·6	0·9
Urinary infection	5·2	3·3
Hypertension and albuminuria ..	12·9	17·0
Hydramnios	3·4	2·3
Prolapsed cord	1·7	0·9
Ante-partum haemorrhage ..	6·0	3·3
Post-partum haemorrhage ..	3·4	5·6
Stillbirth	4·3	2·8
Neonatal death	0·9	1·0

Megaloblastic anaemia tends to occur in older patients and in those who have already had several pregnancies (Figs. 3 and 4). This is in agreement with the reports of other authors although Forshaw (1958) and Giles and Shuttleworth (1958) found a higher percentage of primigravidae than in the present series.

Megaloblastic anaemia of pregnancy is believed to be caused by folic acid deficiency (Chanarin *et al.*, 1959). These authors found that this deficiency often occurs in normal pregnancy and is always present in twin pregnancy. They have demonstrated defective absorption of folic acid in megaloblastic anaemia and to a lesser extent in normal pregnancy. Girdwood (1956) did not find any impairment of folic acid absorption during pregnancy.

The rapidly growing foetus also helps to create a maternal deficiency of folic acid. The high incidence of the disease in twin pregnancy supports this view and Baker *et al.* (1958) found that the serum levels of folic acid and vitamin B_{12} in the foetus greatly exceeded those of the mother in late pregnancy. Maternal deficiency of folic acid is most marked towards the end of pregnancy (Chanarin *et al.*, 1959) and the majority of cases are diagnosed in late pregnancy and the puerperium (Fig. 5).

Dietary deficiency may contribute to maternal deprivation of folic acid. Many dietary studies have been made (Thompson and Ungley, 1951; Ungley, 1952; Lillie *et al.*, 1954; Gatenby, 1956; Giles and Shuttleworth, 1958), but the results are inconclusive. A number of patients had a diet poor in meat and fresh fruit and vegetables but many enjoyed an adequate diet and other women who had a very poor diet failed to develop the anaemia. It is important to note that the grossly inadequate diet described by Tasker *et al.* (1956) in patients with megaloblastic anaemia in the tropics may be encountered in this country. Four patients in the present series were coloured immigrants, who for religious or economic reasons ate mainly rice.

With regard to the role of diet, it is significant that the disease is confined to hospital practice, the patients belonging to the industrial working class (Table III). In contrast, only 1 case was diagnosed in 1,500 private confinements (Craig, 1960). Private patients generally belong to the business and professional classes and normally eat a good diet. They are also intelligent and attend regularly for antenatal supervision compared with the very poor antenatal record of the megaloblastic anaemia patients. Dietary deficiency is not caused by unemployment as 93 per cent of the husbands in the present series were working.

Interference with the metabolism of folic acid by development of an antagonist of endocrine or metabolic nature has been suggested by Badenoch *et al.* (1955) and Girdwood (1956), but this substance has not yet been demonstrated. A deficiency of ascorbic acid can also derange the metabolism of folic acid (Mueller and Will, 1955). Infection, hypertension and albuminuria may interfere with the metabolism of folic acid (Badenoch *et al.*, 1955), but Giles and Shuttleworth (1958) found a very low incidence of infection in their series and the incidence of hypertension and albuminuria was the same as in normoblastic anaemia. The incidence of sepsis is high in the present series (Table IV) and the majority of the incidents preceded the onset of anaemia. Hypertension and albuminuria do not appear to be of much aetiological importance in the present series as their incidence is less than that of the controls (Table IV).

It is clear that the maternal deficiency of folic acid may arise from increasing foetal demand, impaired absorption, dietary deficiency or interference with its metabolism. The importance of each of these factors probably varies from one patient to another and megaloblastic anaemia of pregnancy may not be a single entity, but a group of anaemias each with a different aetiology. This has been suggested by Badenoch *et al.* (1955) and Giles and Shuttleworth (1958). Further study of the absorption and metabolism of folic acid is necessary to elucidate the problem.

There is no evidence that deficiency of vitamin B_{12} plays any part in the pathogenesis of the anaemia. The serum levels are normal and absorption is unimpaired (Badenoch *et al.*, 1955). Treatment with vitamin B_{12} is not always successful (Scott, 1954; Moore *et al.*, 1955).

Gastro-intestinal symptoms were rare in the present series; only 3 patients gave a history of

severe vomiting. Giles and Shuttleworth (1958) obtained a history of vomiting or diarrhoea in 7 out of their 83 patients, but many had anorexia.

It has been suggested that prophylactic folic acid should be given to all pregnant women during the last trimester. However, as facilities for routine blood examination are available throughout the country, prophylactic folic acid should be reserved for patients with anaemia which is not obviously iron deficient or which is not responding to adequate iron therapy.

Summary

One hundred and sixteen cases of megaloblastic anaemia of pregnancy and the puerperium were diagnosed at this hospital during a 4-year period, giving an incidence of 1 in every 92 confinements. One-half of the cases occurred during the puerperium and most of the remainder during the last 6 weeks of pregnancy. The majority were diagnosed between the months of May and November.

The anaemia was not always severe, only 25 per cent of patients had initial haemoglobin values under 7 g. A concurrent iron deficiency was frequently present. Megaloblasts were found in the peripheral blood in 55 patients.

The disease was associated with increasing age and parity and there was a much higher incidence in twin pregnancy.

The anaemia responded well to folic acid and the addition of vitamin B_{12} did not appear to make any difference to the response. Blood transfusion should be reserved for the treatment of haemorrhage or of severe anaemia diagnosed near term.

The pathogenesis of the anaemia is considered. It would appear that it is caused by maternal deficiency of folic acid. As this may arise in a variety of ways, it has been suggested that megaloblastic anaemia of pregnancy and the puerperium is a group of diseases, each with a different aetiology.

Prophylactic folic acid is advised for those pregnant women who have anaemia which is not obviously due to iron deficiency or not responding to adequate iron therapy.

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THE DETECTION OF FOETAL ERYTHROCYTES IN BLOOD SMEARS

BY

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INTRODUCTION

ZIPURSKY, Hull, White and Israels (1959) have described a simple method for the detection of foetal erythrocytes in the blood smears obtained from post-partum mothers. The method was based on the observation of Kleihauer *et al.* (1957), that foetal haemoglobin in red cell smears resisted elution by acid phosphate buffer and retained the property of staining with May-Gruenwald stain. Adult haemoglobin did not retain this property. Zipursky and his co-workers detected small numbers of foetal erythrocytes in 21 per cent of the blood smears obtained from 42 mothers on the second to the sixth day after delivery. No foetal erythrocytes were detected in the smears of 90 blood donors.

This report presents the findings of a study using Zipursky's method. The study included the examination of blood smears from 40 ante-partum mothers as well as 58 post-partum mothers and 100 blood donors.

METHOD

Blood was obtained by finger stab and collected in a small test tube containing a drop of 1/1,000 solution of heparin evaporated to dryness. The blood was diluted 1 in 3 with physiological saline. From this dilution, blood smears were prepared and treated according to the method of Zipursky *et al.*, except that Wright's stain was substituted for the May-Gruenwald stain. An area of uniform density in the smear was selected and examined microscopically with the high power ($\times 400$) objective. One hundred separate fields, each containing approximately 500 erythrocytes, were examined on each smear. Foetal erythrocytes were distinguished from surrounding erythrocytes by their increased size, denser staining, and increased refractility (Fig. 1).

Forty ante-partum patients attending the Outdoor Clinic of the University of Alberta Hospital were examined. In 18 of these patients blood samples were taken on 2 or more visits to the clinic, usually at monthly intervals. In this manner a total of 86 smears were obtained on separate occasions from the 40 ante-partum mothers. The 58 post-partum blood samples were obtained from mothers in the University of Alberta Hospital, usually on the second day after delivery. A control group of blood smears was obtained from 100 apparently healthy adult blood donors of both sexes attending the Red Cross blood donor clinic.

The ease with which foetal erythrocytes could be detected was first tested by an examination of blood smears from healthy infants 24 to 48 hours of age. In 64 such infants the average distribution of foetal to adult erythrocytes was 9 : 1. The lowest ratio obtained was 3 : 2. The differentiation of foetal from adult erythrocytes in these preparations was not difficult. In the 3 study groups the ratio of foetal to adult erythrocytes was usually 1 : 25,000. Considerable care had to be exercised in examining smears

TABLE I

The Incidence of Foetal Erythrocytes in Blood Smears of Ante-partum, Post-partum, and Blood Donor Patients

	No. of Patients	No. of Patients with Foetal Erythrocytes	% Positive for Foetal Erythrocytes
Ante-partum	40	7	18
Post-partum ..	58	10	17
Blood donors	100	2	2

from the study groups, as the risk of overlooking single foetal erythrocytes greatly increased the possibility of observer error. All smears classified as positive for foetal erythrocytes were rechecked by two or more observers.

RESULTS

The blood smears from 7 of the 40 ante-partum mothers were positive for foetal erythrocytes (Table I). The period of gestation was estimated on a gestation chart from the date of onset of the last menses. The periods of gestation at which foetal erythrocytes were detected in the 7 expectant mothers with positive smears were as follows:

16–20 weeks = 3 mothers
32–36 weeks = 1 mother
36–40 weeks = 2 mothers
42 weeks = 1 mother

The blood smears from 10 of the 58 post-partum mothers were positive for foetal erythrocytes (Table I). An analysis of this group of women was made according to parity and type of delivery (Table II). Four of the 9 primiparous women were positive for foetal erythrocytes compared to 6 of the 42 multiparous women. Positive smears were obtained from 3 of the 4 primiparous patients delivered with forceps. The blood smears were negative for foetal erythrocytes in all 5 multiparous women delivered by forceps, and in all 7 women delivered by Caesarean section.

The infants of 9 post-partum mothers with positive smears showed no abnormalities during the first week of life. The tenth post-partum mother with a positive smear gave birth, at 35-weeks gestation, to a female infant weighing 2,750 g. The pregnancy, labour, and delivery were uncomplicated. The estimated maternal blood loss during delivery was 50 ml. The infant was pale and limp following delivery. Her haemoglobin was 13·8 g. per cent at 4 hours of age, and 9·6 g. per cent on the third day of life. She received a blood transfusion of 75 ml. on the third day, and her progress thereafter was uneventful. Three foetal erythrocytes were discovered in the maternal blood smear, a number similar to that in the smears from the other 9 post-partum mothers.

The blood smears from 2 of the 100 blood donors were positive for foetal erythrocytes. The first positive smear was obtained from a male, 51 years of age, suffering from polycythaemia vera. He had been donating blood at frequent intervals for therapeutic reasons. The second individual with a positive smear was a female, 47 years of age, who was reported to be in good health and non-pregnant at the time of donation.

TABLE II

Parity and Type of Delivery in Relation to the Incidence of Foetal Erythrocytes in Blood Smears from Post-partum Patients

	Number of Patients	No. of Patients with Foetal Erythrocytes	Per cent Positive for Foetal Erythrocytes
Spontaneous delivery (42):			
Primiparae	5	1	20
Multiparae	37	6	16
Forceps delivery (9):			
Primiparae	4	3	75
Multiparae	5	0	0
Caesarean section (7)	7	0	0

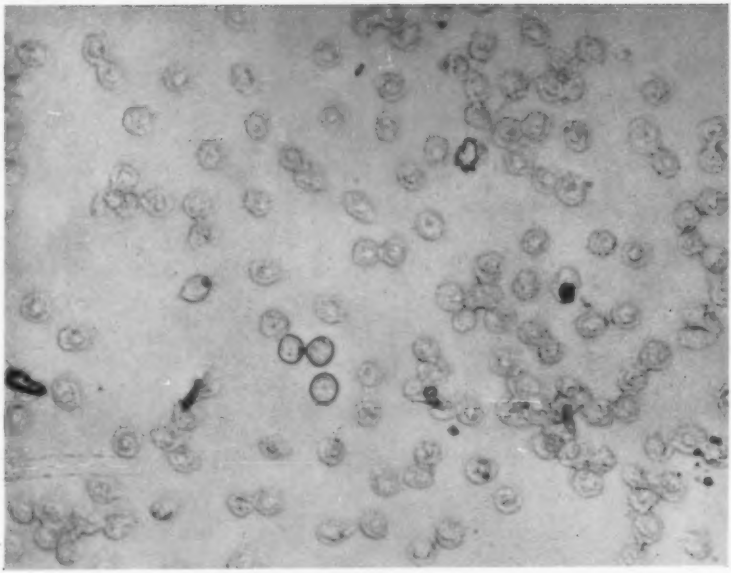

FIG. 1

Post-partum maternal blood. A cluster of 3 darkly staining foetal cells appears in the centre of the field. ×400.

Discussion

The results of this investigation confirmed Zipursky's observation that foetal erythrocytes can be detected in the blood of about 20 per cent of post-partum mothers. There are two possible explanations for this finding. The first is that the mother has manufactured the foetal erythrocytes. The second is that trans-placental passage of foetal erythrocytes from infant to mother has occurred.

The first possibility was supported by the finding of foetal erythrocytes in blood smears from an adult male and from an adult female beyond the child-bearing age. This demonstrated that the ability to manufacture foetal erythrocytes was not restricted to the foetus. The term foetal erythrocyte should not, therefore, be used in the sense that these cells are peculiar to the newborn infant. The term should preferably be used in the sense that foetal erythrocytes are cells of distinct morphology, and that their differentiation from adult erythrocytes depends upon their content of Hb. F.

The second possibility was demonstrated by Chown (1954) with differential agglutination tests which distinguished the antigen of foetal erythrocytes from the antigen of maternal cells in the maternal circulation. It is reasonable to suppose that the transplacental passage of foetal cells would be more common following difficult delivery and would be less frequent following Caesarean section performed prior to the onset of labour. In our group of post-partum mothers only 1 of the 7 mothers delivered by Caesarean section was in labour at the time of operation. The blood smears of all 7 mothers were negative for foetal erythrocytes. In contrast to this group, the 4 primiparous patients delivered with forceps were exposed to the most traumatic form of labour and delivery, and foetal erythrocytes were detected in 3 during the post-partum period.

These observations, however, do not provide an explanation for the presence of foetal erythrocytes in the 10 post-partum mothers. If trans-placental passage was the responsible mechanism then it could be expected that more post-partum mothers would have positive smears than ante-partum mothers. This could not be confirmed from our observation that 18 per cent of ante-partum mothers and 17 per cent of post-partum mothers had positive smears.

The technique which we have used lacks the specificity of differential agglutination techniques. In addition, it is a technique lacking in precision and of limited application in clinical diagnosis. It does, however, confirm the fact that about 20 per cent of pregnant women contain foetal erythrocytes in their blood.

Summary

Blood smears from blood donors, ante-partum and post-partum mothers, have been examined for the presence of foetal erythrocytes by a similar technique to that described by Zipursky *et al.* (1959). Blood smears were positive for foetal erythrocytes in 2 out of 100 blood donors. One of the donors was a 47-year-old female in good health at the time of donation. The other donor was a 51-year-old male suffering from polycythaemia vera who was donating blood at weekly intervals.

The blood smears from 18 per cent of 40 ante-partum mothers, and from 17 per cent of 58 post-partum mothers were positive for foetal erythrocytes. In the post-partum group, the highest incidence of positive smears occurred in primiparous patients following forceps delivery. No foetal erythrocytes were detected in post-partum blood smears from 7 patients delivered by Caesarean section.

These observations suggest that the presence of foetal erythrocytes in the circulating blood is not restricted to the newborn infant, or to the post-partum mother. The term foetal erythrocyte should be used with reference to the morphology of the cell which depends on its content of foetal haemoglobin.

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SERUM ISOCITRIC DEHYDROGENASE IN NORMAL AND ABNORMAL PREGNANCY

BY

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INTRODUCTION

ATTEMPTS to demonstrate leakage into the blood of enzymes presumed to come from infarcted placenta have produced conflicting results. For instance, Borglin (1958) found elevations of serum glutamic oxalacetic transaminase in 6 out of 20 cases of pre-eclampsia. Serum lactic dehydrogenase has been used by several investigators. Little (1959) found no alteration during pregnancy, but a slight rise in labour. Cases of pre-eclampsia were mostly normal during pregnancy, but the rises in labour were higher than in normal labour. Hagerman and Wellington (1959) found a 50 per cent increase in lactic dehydrogenase in the last six weeks of normal pregnancy. Levels fell to normal rapidly after delivery. Heinback and Prezyna (1960) found no alteration during normal pregnancy, but some increase during and just after delivery.

Isocitric dehydrogenase was chosen for investigation as the placenta is a rich source of this enzyme, and normal serum contains only traces. Although present in most tissues, elevations have been found only in association with acute liver disease, but not with myocardial infarction and kidney disease (Sterkel, Spencer, Wolfson and Williams-Ashman, 1958; Kerpola, Nikkila and Pitkanen, 1959). In both these investigations normal levels were found in normal pregnant women. Some preliminary results have been published (Dawkins, MacGregor and McLean, 1959) and communicated to the recent symposium on Eclampsia and Pre-eclampsia of the International Society of Geographical Pathology (Dawkins and Wigglesworth, 1960).

METHODS

Determinations of serum isocitric dehydrogenase were made at weekly intervals, using a modification of the method of Wolfson and Williams-Ashman (1957) in 50 women with normal blood pressures and in 77 women with pre-eclampsia. Measurements were also made in cases of essential hypertension, twins, accidental haemorrhage and other abnormalities.

Triphosphopyridine nucleotide (TPN) and sodium isocitrate were products of the Sigma Chemical Co., St. Louis, Missouri.

Assay System. The components of the system were as follows: Tris buffer pH 7·4, 0·033M; TPN 0·0001M; sodium isocitrate 0·00017M; sodium chloride 0·015M; manganese sulphate 0·001M; serum 0·5 ml., made up to a final volume of 3 ml. with water. The components, with the exception of TPN, were pre-incubated at room temperature for 30 minutes, because of initial changes in turbidity on dilution of serum. The reaction was started by the addition of TPN to one tube and read against a blank containing all components except TPN, by following

the increase in adsorption at 340 mμ in a Unicam SP 500 spectrophotometer using silica cells with a 1 cm. light path at 20°. Readings were made at frequent intervals for at least 30 minutes and were linear with time. Results are expressed in the same arbitrary units as used by Wroblewski and La Due (1955) for transaminase, where 1 unit is the amount present in 1 ml. of serum causing an increase in adsorption at 340 mμ of 0·001 per minute.

Results

(1) *Normal Women*

Seventy-five determinations were made in 50 pregnant women with normal blood pressures. They were mostly primigravidae and the results are shown in Figure 1. Weekly serial determinations in the same patient gave reasonably consistent results. The upper limit of normal is taken as 3·2 units, which is the mean plus two standard deviations. Only one reading during pregnancy fell outside this range, in an elderly postmature primigravida. It can be seen that there is no increase in serum isocitric dehydrogenase up to and past term, although there does seem to be a slight increase during labour. There were no stillbirths in this group and the average placental weight was 550 g. (Range 410–820 g.)

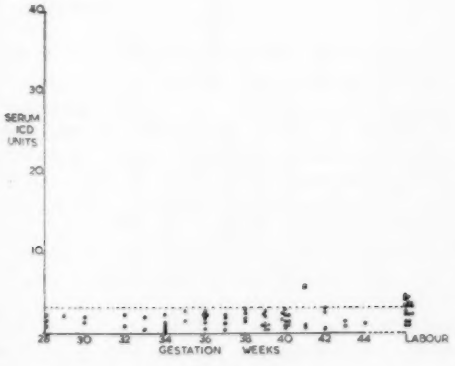

FIG. 1

Serum isocitric dehydrogenase levels in 50 women with normal blood pressures.

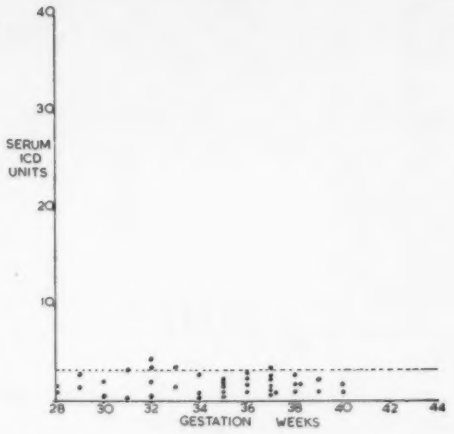

FIG. 2

Serum isocitric dehydrogenase levels in 12 women with essential hypertension.

(2) *Essential Hypertension*

Forty-one determinations were made in 12 women diagnosed as having essential hypertension. These patients had a raised blood pressure at twelve weeks and showed no evidence of superimposed pre-eclampsia. From Figure 2 it can be seen that there is no difference from the normal group. There were no stillbirths in this group and the average placental weight was 520 g. (Range 330–680 g.)

(3) *Pre-eclampsia*

Figure 3 shows the results of 94 determinations in 48 women with mild hypertension developing for the first time during the last trimester. Many of these cases might not be regarded as genuine pre-eclampsia, as none of them had albuminuria and elevations of blood pressure over 140 mm. systolic, 90 mm. diastolic were transient. There was one stillbirth during labour in this group. The average placental weight was 530 g. (Range 305–680 g.) It can be seen that here also there is no significant rise in serum isocitric dehydrogenase during pregnancy, but that values in labour tend to be higher than in normotensives.

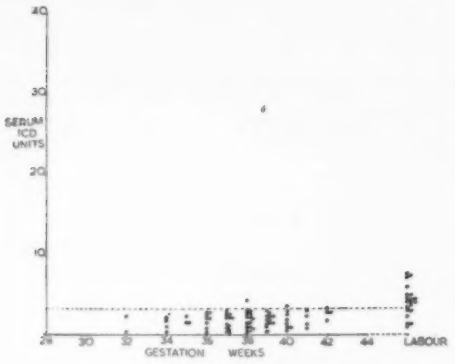

FIG. 3

Serum isocitric dehydrogenase levels in 48 women with mild pre-eclampsia.

Figure 4 shows the results of 45 determinations in 17 women with clinically severe pre-eclampsia. There were 4 stillbirths in this group and the average placental weight was 405 g. (Range 270–670 g.) All the serial determinations in these cases are included, some of them made before the onset of clinical deterioration. It can be seen that many readings are above normal. Sixteen of these 17 cases had one or more transient elevations in serum isocitric dehydrogenase accompanying a recent increase in diastolic blood pressure. One of these 17 cases had normal readings at four weekly intervals with clinically severe pre-eclampsia; her placenta was extremely small and showed very extensive old infarction. None of these cases showed any evidence of accidental haemorrhage.

Figure 5 shows the changes in serum isocitric dehydrogenase in a typical incident, in which there was a sudden rise of 25 mm. in diastolic pressure with the development of albuminuria. Serum isocitric dehydrogenase is initially normal, rises sharply and quickly returns to normal. In this case labour was induced, but a similar pattern is seen if placenta and foetus remain *in utero*. It is suggested that placental infarction is the source of this enzyme for the following reasons: elevated levels are always found in cord blood whenever they are present in maternal blood and after delivery levels always fall to normal in two or three days. Two out of the total of 77 women with pre-eclampsia examined did not conform to this pattern of a transient rise in serum isocitric dehydrogenase

FIG. 4

Serum isocitric dehydrogenase levels in 17 women with severe pre-eclampsia.

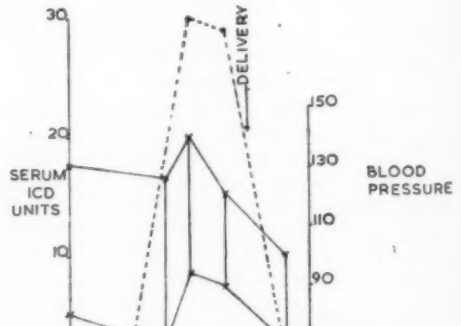

FIG. 5

Changes in serum isocitric dehydrogenase associated with a sudden rise in diastolic blood pressure.

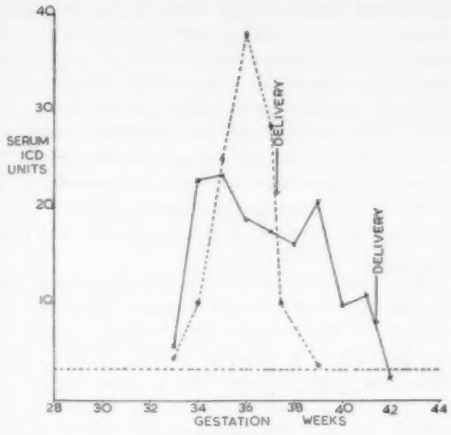

FIG. 6

Prolonged elevation of serum isocitric dehydrogenase in two cases of pre-eclampsia.

accompanying deterioration in clinical condition. They both showed considerable elevations of serum isocitric dehydrogenase as shown in Figure 6, in the last weeks of pregnancy with signs of moderate pre-eclampsia developing about the thirty-second week without fluctuations in blood pressure. Levels returned to normal after delivery. Neither case showed any clinical evidence of liver disease, although one case had a urinary infection which responded to treatment.

(4) *Miscellaneous Abnormalities of Pregnancy*

Cases of accidental haemorrhage are also accompanied in most cases by a rise in serum isocitric dehydrogenase. Table I shows the values in 9 cases during the episode of bleeding. Seven out of 9 showed elevated readings. Raised levels at some time were also found in 4 out of 5 women with a previous stillbirth associated with pre-eclampsia, but with normal blood pressure during the present pregnancy. Table I also shows the highest readings obtained in these 5 cases. Normal values were obtained in 4 cases of twins with normal blood pressure, 2 cases of rhesus incompatibility with normal blood pressure and one case of diabetes with normal blood pressure.

TABLE I

Maximum Serum Isocitric Dehydrogenase Levels in 7 Women with Accidental Haemorrhage and in 5 Women with Previous Stillbirths

Accidental Haemorrhage	Previous Stillbirths
5·7	5·3
6·7	4·7
2·0	12·3
3·8	4·6
4·0	1·5
3·3	
12·0	
3·8	
4·3	

(5) *The Placenta*

A careful macroscopic examination of serial 1 cm. slices of the placenta after at least 7 days fixation in formalin was made in 40 of the cases of pre-eclampsia and 10 of the normal cases with histological examination of at least four representative blocks. All those with elevated readings showed true infarction of villi, and the mean placental weight in this group was considerably less than in other groups. However, infarction was often found in the placentae of women with pre-eclampsia with normal serum isocitric dehydrogenase, and in some normal women, but it tended to be much less extensive. No attempt was made to estimate this difference in quantitative terms. Presumably transient elevations might easily be missed with serial determinations at weekly intervals.

DISCUSSION

Leakage of isocitric dehydrogenase into the blood is the earliest detectable manifestation of experimental injury to the liver cell, and occurs several hours before there is any visible sign of damage (Rees, Spector and Sinha, 1960). It is generally agreed that there is a reduction in blood flow throughout the intervillous space in pre-eclampsia (Browne and Veall, 1953). This is probably due to obliterative lesions in the maternal vessels to the placental bed (Dixon and Robertson, 1958). The result is ischaemia of the placenta and an increased perinatal mortality. The increase in perinatal mortality

is directly related to the severity of the pre-eclampsia (Claireaux, 1960).

We have shown that in cases of severe pre-eclampsia there are often transient rises in serum isocitric dehydrogenase. In such cases there is generalized spasm of blood vessels which might produce focal ischaemia in many organs. However, we suggest that the placenta is the source of these transient elevations, since levels always fall after delivery and the enzyme is always present in cord blood when the maternal level is raised. Moreover, the level in cord blood is always somewhat higher than in maternal blood.

There have been many conflicting studies of the significance of degenerative lesions in the placenta in relation to pre-eclampsia. Tenney and Parker (1940) and more recently Shanklin (1959) have suggested that a diffuse degeneration and shedding of the syncytiotrophoblast is the most important lesion and that infarction has no significance. Little (1960) has reviewed the extensive literature on this subject and has made an extremely detailed and careful analysis of 1,000 placentae. He came to the conclusion that there is a good correlation between severe pre-eclampsia and extensive true infarction. The association between severe pre-eclampsia and transient elevations in serum isocitric dehydrogenase would support this, and indicates that in most cases the process of degeneration is by episodic infarction rather than continuous slow degeneration.

Normal pregnancy, pregnancy complicated by essential hypertension and cases of mild pre-eclampsia do not show any increase in serum isocitric dehydrogenase even in postmature pregnancy. This is in contrast to the results of Hagerman and Wellington (1959) for lactic dehydrogenase, but in agreement with the results of Little (1959) with the same enzyme. Both Little (1959) and Heinback and Prezyna (1960) recorded elevations in labour. We, too, have found elevations in labour, cord blood always containing somewhat higher levels than maternal blood. We suggest that even during normal labour there is sufficient placental ischaemia to produce a rise in serum isocitric dehydrogenase in maternal and cord blood.

Elevations of serum isocitric dehydrogenase were also commonly found in association with accidental haemorrhage. This is also in agreement with the findings of Little (1959) with serum lactic dehydrogenase. Areas of premature placental separation often show adjacent infarction, which is presumably the source of this rise. The presence of transient elevations in serum isocitric dehydrogenase in women with a history of previous stillbirth is interesting in view of the increase in abnormalities in subsequent pregnancies (Conway, 1951), in such women.

The source of serum isocitric dehydrogenase in the two cases with prolonged elevation is a matter of speculation. Degenerating syncytiotrophoblast is a possible source. It is at any rate clear that the syndrome of pre-eclampsia is not entirely homogeneous in this respect. Little (1959) has also reported one case of prolonged elevation of serum lactic dehydrogenase in a woman with pre-eclampsia.

It must be emphasized that the presence of a transient rise in serum isocitric dehydrogenase in a woman with pre-eclampsia is only evidence of placental degeneration at that moment. It gives no indication of placental reserve. However, it does emphasize that there is a very close temporal relationship between sudden rises in diastolic pressure and placental infarction. Whether the vasospasm accompanying a rise in diastolic pressure is the cause of placental infarction, or whether infarcted placenta is in some way responsible for a rise in blood pressure is a matter for further investigation.

Summary

Serum isocitric dehydrogenase levels do not alter in normal pregnancy, pregnancy complicated by essential hypertension or mild pre-eclampsia. Transient elevations of serum isocitric dehydrogenase occur in cases of severe pre-eclampsia at the time of fairly sudden clinical deterioration. Elevations are also found in cases of accidental haemorrhage and in women with previous stillbirths. It is suggested that placental infarction is the source of this enzyme.

It is a great pleasure to acknowledge the advice and co-operation of Professor W. C. W. Nixon and the staff of the Obstetric Hospital,

University College Hospital. Our thanks are due to Sir Roy Cameron, F.R.S., for his interest and encouragement. The expenses of the investigation were met from the Graham Research Fund of the University of London and the Research Fund of University College Obstetric Hospital.

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CONSERVATIVE TREATMENT OF PARTIAL PLACENTA PRAEVIA-ACCRETA

Report of a Case

BY

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PLACENTA accreta rarely can be treated conservatively and only, as a rule, when the pathological adherence is either complete or involves a very small portion. The unusual, and fortunate, circumstances met with in the following case of partial placenta praevia-accreta permitted conservation of the uterus at the time of Caesarean section.

Case Report

Mrs. M.W., a primigravida, aged 20 years, was referred to the antenatal clinic at the Royal Maternity Hospital, Glasgow, on 8th August, 1958, on account of a suspected breech presentation. She was then 36-weeks pregnant, the expected date of delivery being 2nd September, 1958.

She was a healthy, attractive girl who had kept well throughout the pregnancy. Apart from diphtheria at the age of 10 years she had had no serious illnesses. The only previous operation had been tonsillectomy at the age of 2 years.

On examination, the uterus was enlarged to the size of a 36-weeks pregnancy, the lie of the foetus was longitudinal and the vertex was presenting free above the pelvic brim. Vaginally, the pelvic measurements were normal. While checking the vertex presentation by palpating the foetal head through the fornices, strong pulsation was felt in the left fornix associated with a structure which felt very like the umbilical cord. The pulsations were similar in rate to the foetal heart sounds which were 132 beats per minute.

A provisional diagnosis of cord presentation was made and the patient was immediately admitted as the cervix was partly effaced and the external cervical os was two-fingers dilated.

Under general anaesthesia a further vaginal examination was made in the operating theatre. The pulsations in the left fornix could still be felt. The cervix admitted two fingers and pulsating cord could be felt directly over the os and passing to the left side. On attempting to trace the cord to the right side, the edge of the placenta was encountered extending down to the margin of the internal cervical os and some fresh bleeding commenced. A cord presentation with type *ii* placenta praevia was diagnosed and Caesarean section was performed immediately. On opening the lower uterine segment, the placenta was encountered on the right half of the incision and it had to be cut through. It was noted at that time that the wall of the lower segment on the right side where the placenta was attached was very thin.

A premature female child weighing 5 pounds 3 ounces was easily delivered by the vertex and the child cried shortly after birth. Following the delivery of the child, 0·5 milligrammes of ergometrine were given intravenously.

The cord could be seen lying across the internal os and coming up the left side of the uterus. The placenta was situated mainly on the right side of the uterus, with part of it encroaching on to the posterior wall and a large

FIG. 1

Photograph of the biopsy specimen. Some placental villi can be seen attached to the wall of the lower segment. ×6.

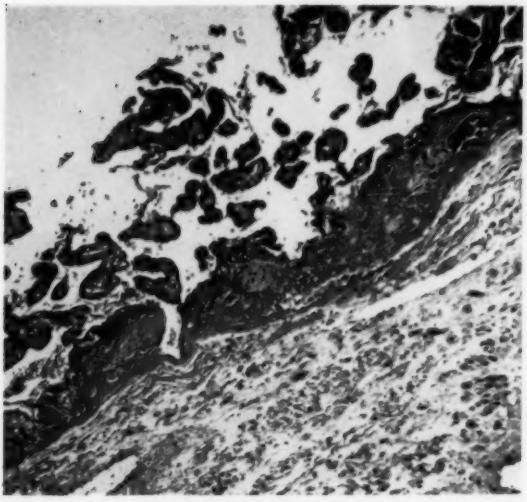

FIG. 2

Low power photomicrograph. ×60.
Muscle of lower segment clearly seen, separated from the chorionic villi by a dense layer of fibrin representing Nitabuch's fibrin stria. No decidua seen, nor any significant hyalinization of the uterine muscle.

part extending round on to the anterior wall as far as the midline in the lower segment. The lower edge of the placenta extended to the margin of the internal cervical os and the cord was attached to the placenta at this point. The placenta was easily separated and removed from the upper segment, but the part occupying the lower segment could not be separated and no plane of cleavage could readily be found. Some of the placental tissue was incompletely torn off the posterior wall of the lower segment with considerable difficulty and it was then realized that the condition was a partial placenta accreta. The already separated placenta was detached from the adherent remainder and removed. The lower segment was inspected and about one quarter of the placenta was still attached round the right side. The placenta was thinner than normal and had penetrated the wall of the lower segment to some extent as the cut edges of the lower segment on the right side consisted mostly of placental tissue with thinned out uterine wall.

There was brisk bleeding coming from the posterior wall of the lower segment following the attempts to remove the placenta. The patient was showing signs of blood loss so blood transfusion was commenced. In the hope of avoiding hysterectomy, especially as the bleeding points were reasonably accessible, several haemostatic catgut sutures were inserted into the posterior wall of the lower segment, checking with the hand behind the uterus that the stitches did not pass right through the wall and inadvertently catch any bowel in the pouch of Douglas. A small section from the edge of the lower segment incision was removed for histological examination. All bleeding was eventually stopped and the lower segment was closed, incorporating the adherent placental tissue at the cut edges in the first continuous catgut suture, and burying this suture line with a second continuous catgut suture in the usual manner. The lower segment was then peritonized and the abdomen closed in layers. The ergometrine was repeated at the end of the operation and again 20 minutes later as some vaginal bleeding was persisting. Thereafter, bleeding ceased and the patient's condition was satisfactory. A total of 2 pints of Group A Rhesus negative blood and 1 pint of 5 per cent dextrose were given. The patient was closely observed for several hours after operation and fortunately no fresh bleeding occurred.

The post-operative recovery was uncomplicated. The lochia remained normal and involution of the uterus proceeded satisfactorily. Intramuscular iron therapy was given for post-operative anaemia. The baby was breast-fed and progressed satisfactorily. The mother was allowed home on the fifteenth day of the puerperium.

On examination at the postnatal clinic 6 weeks later, the patient was very well and there had been no coloured lochial discharge since the 12th day after the operation. On vaginal examination, the involution of the uterus was most satisfactory, its size being little larger than normal.

Histology

The biopsy specimen taken from the lower uterine segment is illustrated in the accompanying figures (Figs. 1 and 2). At the utero-placental junction no decidua is seen and there is a dense layer of fibrin between the chorionic villi and the uterine muscle.

Discussion

In cases of placenta accreta there is a relatively high incidence of implantation of part or all of the placenta in the lower uterine segment (Millar, 1959).

The present case shows clearly that the accreta portion of the placenta can be confined to the lower segment and this may be accounted for by the poorer formation of the decidua in that area.

The cause of placenta accreta is not so easily explained, however, as partial placenta accreta may occur in the upper segment and be limited to as small an area as one cotyledon. The writer has recently had the opportunity of studying in detail a specimen of partial placenta increta with the following findings. In the upper segment there were areas where placental attachment was normal, with plentiful decidua, and the placenta could be separated easily. Other areas showed

absence of decidua with varying degrees of penetration of the uterine muscle by the villi, and in these areas the placental tissue could not be separated even when the excised uterus was examined in the laboratory. It is difficult to explain the aetiology of such patchy decidual deficiency. Examination of the villi did not reveal any histological evidence that might suggest excessive trophoblastic invasiveness.

The opportunity for conservative treatment, as carried out in the present case, does not often arise, but the easy access to the abnormal area in the lower uterine segment allowed satisfactory haemostasis and closure to be achieved without difficulty.

In the treatment of cases of placenta praevia it has been stressed by Macafee (1960) that the surgeon may meet with difficulties during Caesarean section. Placenta accreta is one of these and all Caesarean sections needed for placenta praevia should be carried out, if possible, by experienced obstetricians operating under ideal conditions.

Summary

(1) A case of partial placenta praevia-accreta treated by Caesarean section and conservation of the uterus is described.

(2) The accreta portions of the placenta were confined to the lower uterine segment supporting the view that decidual deficiency in that area predisposes to abnormal placental attachment.

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SPONTANEOUS RUPTURE OF THE UTERUS DUE TO PLACENTA PERCRETA

A Case Report

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MANY of the circumstances leading to rupture of the uterus in labour are foreseeable and therefore preventable; the condition is thus less common than in the past. There are, however, a number of unavoidable causes, one of which is the erosion of the myometrium by the placenta. An example of this rare condition recently occurred at the Middlesex Hospital.

Case History

Mrs. A.B. attended the hospital during her second pregnancy when she was aged 36. Her first pregnancy, 18 months previously, was normal and she began labour at term. The first stage of labour was normal. Foetal distress became apparent in the second stage. The child was delivered by forceps without difficulty, but was stillborn; it weighed 5 pounds 11 ounces. The placenta was retained and had to be removed manually; it was not felt to be abnormally adherent. There was a velamentous insertion of the cord, but no bleeding which could account for foetal distress had occurred. Post-mortem examination of the child showed the signs of asphyxia without other abnormality. The mother made an uneventful recovery.

The second pregnancy was again uneventful; she had no abnormal symptoms and made no complaint of abdominal pain. She was admitted to hospital, in labour, at term. She had no abdominal pain apart from that due to the contractions. The vertex was presenting with the head engaged; the foetal heart rate was normal.

Some two hours after admission she vomited, became restless and complained of hypogastric pain. She appeared pale, was sweating and collapsed. There was marked tenderness on palpation of the lower abdomen. The foetal heart rate was now 90 per minute. Vaginal examination showed the cervix to be dilated to two or three fingersbreadth. The clinical picture suggested uterine rupture or an accidental haemorrhage. As the child was still alive, it was decided to perform Caesarean section immediately. An intravenous infusion was started and the patient was anaesthetized.

On opening the abdomen, a large quantity of fresh blood was found. There was no sign of rupture of the exposed part of the uterus, nor was there haematoma formation in the broad ligaments. A lower segment Caesarean section was performed and the child delivered: it was stillborn. The uterus was then brought out of the abdomen and examined. On the left side of the fundus, just medial to the attachment of the Fallopian tube, there was a dome-shaped protuberance, covered only by peritoneum, which could be seen to contain placental tissue; it measured about 2 inches $\times 1\frac{1}{2}$ inches. At its summit there was a small tear, through which blood was escaping. Examination through the uterine cavity showed that the placenta was firmly adherent in the region of this protrusion; it appeared that this was a case of placenta percreta.

The patient had now lost two children and it was known that she was particularly anxious to have a child; it was felt that the uterus must be preserved, especially as the alternative of hysterectomy could not then be discussed with her. An incision was made through normal uterine muscle around the protrusion and the placenta with its covering of peritoneum was excised.

The incision in the fundus was repaired, the lower segment incision was sutured, and the abdomen closed. During the operation and the immediate post-operative period, a transfusion of one pint of Dextran and six pints of blood was given. She responded well to this resuscitation; her blood pressure when she returned to the ward was 110/70 mm. Hg. Her recovery was uneventful and she was discharged 13 days after the operation. When she returned to the out-patient clinic two months later, she felt well and her condition was satisfactory. She has not yet become pregnant again.

Pathology

Examination of the placenta and excised myometrium showed herniation of the placenta through thinned uterine wall. The decidua was absent at the point of adherence of the placenta, with direct invasion of the muscle by chorionic villi; there was considerable fibrosis in the surrounding muscle. These findings are characteristic of placenta percreta.

Discussion

Incidence

Morbid adherence of the placenta is uncommon; spontaneous rupture of the uterus due to this condition is rare.

Kaltreider (1945) reviewed 73 reported cases of placenta accreta and found 11 cases of spontaneous rupture of the uterus. We found 19 cases in the literature where an otherwise normal uterus had ruptured, 2 where the uterus showed congenital abnormality and 2 where the placenta had perforated the scar of a Caesarean section. In 2 other cases, those of Fitzgerald, Webster and Fields (1949) and Svanberg (1949), it is difficult to assess the importance of morbid adherence of the placenta in causing the rupture of the uterus; in the first case the whole uterus is described as being "paper-thin", in the second case there had been two intra-uterine manipulations before laparotomy.

Aetiology

The basic lesion in placenta percreta is absence of the basal layer of the decidua. It has been suggested that this may be the result of endometrial deficiency caused by previous trauma or sepsis. Irving and Hertig (1937) found a possible cause of such damage in 43 per cent of their cases, manual removal of the placenta being the commonest; most authors record incidents such as curettage, endometritis or intra-uterine obstetric manipulations in their case histories.

Cuthbert (1956) stresses the importance of sepsis as a causal factor and believes it to be more important than trauma. In many cases, however, there is no evidence of sepsis after manual removal of the placenta; there was none in our patient's first pregnancy. Clerc (1947) quoted a morbidity rate of 12 per cent in a series of manual removals and this included cases of thrombosis and pulmonary embolism. Sepsis is not a common sequel to curettage apart from cases of septic abortion.

Millar (1959) states that "if previous trauma and infection did influence the development of placenta accreta, it would occur more frequently than it does, considering the many thousands of manual removals and curettages done every year".

In most of the cases of placenta percreta where curettage was a possible cause, it should be noted that it had been performed for the removal of placental tissue following delivery or abortion; it may be, as Irving and Hertig (1937) suggest, that there was a morbid adherence of the placenta in the previous pregnancy and that the causal role of curettage is more apparent than real. It does seem probable that the underlying cause, as believed by Millar, is a primary decidual deficiency.

Clinical Features

In our case, as in that of Martini (1956), rupture of the uterus occurred after labour began at term; Pettit and Mitchell's case (1949)

FIG. 1
An artist's impression of the uterus at operation.

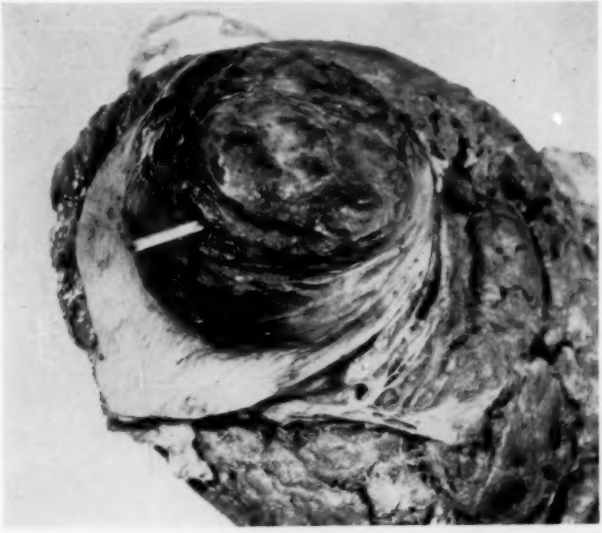

FIG. 2
The site of rupture, indicated by the pointer.

FIG. 3
Microphotograph of the junction of the placenta and myometrium. ×75.

showed the signs during labour at the 37th week. It is not surprising, however, because of the nature of the lesion, that the erosion of the myometrium may cause rupture before labour and earlier in pregnancy, in the case of Taylor *et al.* (1958) as early as the 20th week

McKeogh and D'Errico (1951), state that "labour-like" contractions during pregnancy are a feature of placenta percreta. Several of the reported cases where rupture occurred gave a history of abdominal pain during the pregnancy and a prodromal stage of discomfort before the severe pain and collapse which followed the rupture. Such symptoms in a patient giving a history of one of the predisposing causes discussed should suggest the possibility of this condition. The sudden onset of severe pain and shock may, however, be the first signs, as in our case.

The physical signs are those of haemoperitoneum, with localized tenderness over part of the uterus in some cases. The picture may resemble that of concealed accidental haemorrhage and this may cause a delay in making the decision to operate, particularly when the foetal heart cannot be heard; consideration of the history may provide a guide in such circumstances.

The commonest site of rupture is at the fundus; this is usually described as being replaced by the placental mass covered by peritoneum. In other cases the rupture has been in the lower segment (Bakanow, 1928), the posterior wall (Bortkewitsch, 1911), and the anterior wall (Martini, 1956): in Martini's case there was a second tear in the left side of the uterus.

It does not appear that the extent of the morbid adherence of the placenta has any bearing on the likelihood of uterine rupture; complete and partial placenta percreta have been found with about equal frequency in these cases.

Treatment

When the abdomen has been opened and the condition found, there are three possible methods of treatment:

(*i*) Hysterectomy.
(*ii*) Repair of the uterus.
(*iii*) Repair of the uterus with ligation of the tubes.

Hysterectomy is the method which has been most commonly carried out and advocated. It is true that this is the safest course; the immediate risk should be small if resuscitation is adequate and the remote risk of rupture in future pregnancy is abolished. If the patient has children and is not particularly anxious to have more, this is the treatment of choice; it would also seem advisable in cases of total placenta percreta, where removal of the whole placenta and safe repair of the uterus would be difficult.

We do not feel that repair of the uterus combined with sterilization has any great advantage, apart from the possible psychological benefit to some women of preservation of the uterus; from the point of view of operative risk in an ill patient, it is no less shocking than hysterectomy.

If the patient is childless and the case is one of partial placenta percreta, preservation of the uterus with the chance of further pregnancy is obviously desirable and would seem to be justifiable. Placenta percreta does not necessarily recur and has been followed by normal pregnancy (Schuman, 1940; Muir, 1948). The dangers of rupture of the uterus in a future pregnancy could be lessened considerably if the patient were kept in hospital for, say, the last half of pregnancy so that immediate treatment could be given if rupture occurred. Elective Caesarean section, performed at the 38th week, would shorten the period of risk and eliminate the danger of rupture during labour.

The decision on the method of treatment has to be made during an emergency operation, when there has been no opportunity of discussing with the patient the alternatives and the risks involved. We think that it is wrong to perform hysterectomy on a young woman under these circumstances. The patient should be given the option of taking the risks of further pregnancy if she feels inclined to do so; if she decides, after unhurried consideration, that she cannot accept the risks, it is justifiable to perform sterilization at a second operation.

Summary

(1) A case of spontaneous rupture of the uterus due to placenta percreta is described.

(2) The reports of similar cases in the literature are reviewed.

(3) The methods of treatment are discussed.

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USE OF METHOTREXATE IN SECONDARY CHORIONEPITHELIOMA

Report of a Case

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Magna Pars Est Profectus Velle Proficere.
—SENECA, *Letters to Lucilius*, 71.

INTRODUCTION

IGNORANT of the potency of Methotrexate in the treatment of secondary chorionepithelioma and allied conditions, I was well out in the poor prognosis I gave to the Medical Superintendent of Footscray Hospital, when he rang me in late November, 1959, about one of my patients who had a vaginal secondary from a primary chorionepithelioma. I did not then expect the patient to be alive and well six months later.

CLINICAL HISTORY

Mrs. J. was 31 years old; she had two children aged 10 and 8 years. She had been in Footscray Hospital twice in 1956 with incomplete abortion; both times she was curetted, but neither specimen was examined histologically.

In June, 1959, she miscarried at 3 months and was curetted, the pathologist reporting necrotic decidua.

In July, 1959, when seen at Out-patients, the uterus was 12 to 14 weeks in size. She had had slight vaginal loss, and, as the os was still closed, she was thought to be either pregnant or to have a hydatidiform mole. The toad test was positive in undiluted urine only.

In August, as the loss persisted, she presented at Casualty with heavy vaginal bleeding. The os was now open and curettage was performed with the uterus 16 weeks in size. The toad test done the following day was positive again in only undiluted urine.

PATHOLOGY REPORT

"The curettings consist of abundant material which is mostly necrotic, but in some areas consists of recognizable trophoblast. Both cytotrophoblast and syncytiotrophoblast are recognizable, the latter forming large masses of vacuolated cytoplasm with large bizarre nuclei. No villi are present. Chorionepithelioma."

FURTHER MANAGEMENT

Five days later, 10th August, 1959, total hysterectomy and bilateral adnexectomy was performed. There were no apparent abdominal metastases. The toad test, still positive in undiluted urine only, became negative three days after operation. Her convalescence was hastened by blood transfusion and she was discharged two weeks later.

PATHOLOGY REPORT OF UTERUS AND ADNEXAE

"This mass is largely necrotic, but it contains islands of mixed cytotrophoblast and syncytial trophoblast. These cell groups are confined to the walls of thin blood vessels without any invasion of the myometrium away from the vessels, and in this respect the tumour is more suggestive of an invasive mole than a chorion carcinoma. Tubes and ovaries normal."

FOLLOW-UP

Mrs. J. was regularly seen at our Out-patients and repeated toad tests remained negative. On 16th November, 1959, i.e., three months from operation and diagnosis, she presented with vaginal bleeding, and a large secondary deposit, the size of a plum, was seen on the left lateral vaginal wall, half way down the vagina.

She was admitted to hospital. Toad test was now positive in undiluted urine only. Chest X-ray was negative. It was then decided to commence Methotrexate therapy.

Methotrexate Treatment

Mrs. J. was admitted on 16th November. Blood, liver and urinary investigations were done, while awaiting delivery of this restricted drug.

(a) *Chemical formula.* Chemically Methotrexate is 4 amino N^{10} methyl pteroylglutamic acid.

(b) *Action.* It is a folic acid antagonist. Folic acid is pteroylglutamic acid, and is essential for nucleic acid formation. Methotrexate stops the formation of folic acid into folinic acid—folinic acid being otherwise known as the citrovorum factor.

Folic acid is essential for the growth of the female genital tract and for normal embryonal development and, as chorionepithelioma is a malignancy of embryonal tissue, it was decided to use a folic acid antagonist in the treatment of the metastases in this case.

(c) *Mode of Administration.* It may be given orally, intramuscularly or intravenously and the dosage is decided by body weight, but an average dosage has been 2 tablets (1 tablet=2·5 mg.) 5 times a day for 5 days—a total of 125 mg. per course.

(d) *Toxic Effects.* Methotrexate is a very potent drug and its administration needs careful control. The main toxic effects are seen in the blood—leucopenia and anaemia; in the alimentary canal—stomatitis, glossitis, anorexia, pharyngitis, vomiting and diarrhoea; and in the liver—jaundice and liver failure.

The maximum effects are not noted until the course is completed, and as the effects are mostly reversible, and not related to the withdrawal of the drug, there is no treatment other than time. Another course cannot be commenced until the blood picture and the alimentary canal are normal. The patient above developed all of these complications except jaundice and liver failure.

(e) *Number of Courses.* Hertz *et al.* (1958) have one patient who needed 22 courses to keep her free from recurrence.

(f) *Results.* Hertz *et al.* (1958) and Li, Hertz and Bergenstal (1958) have reported 29 cases treated with Methotrexate. All cases have been proven histologically, radiologically, clinically and hormonally and one case is alive and well, free from recurrence after 29 months.

(g) *Results in Patient Described.* Methotrexate was commenced on 30th November, 1959 as oral tablet, 2 five times daily for 5 days.

Within three weeks there was obvious regression of the tumour, originally the size of a plum. While on the drug the secondary bled torrentially on two occasions, needing vaginal packing and blood transfusion. She was allowed home for Christmas and, when seen in Out-patients in January, 1960, there was no lesion detected in the vagina. There was a pitted scar only.

Again in February, March and April the vagina was apparently normal; the toad test was negative and the patient was very well in all respects.

Discussion

It is often very difficult to differentiate chorionepithelioma from chorioadenoma destruens or invasive mole, and in this case the curettings revealed the former, whereas the uterine specimen was more in favour of the latter.

It is known commonly that with mole or malignancy, the titre of gonadotrophin is very high as reflected in the positive tests obtained in diluted urine. Indeed, it is often stated that, unless the toad or other urinary tests are positive in dilution, then the case is not a mole or a chorionepithelioma.

This patient proves the exception, for at no stage was the urine test positive in diluted urine. This can be explained by the great amount of necrotic tissue in the tumour which may fail to secrete gonadotrophin.

It is known that patients with invasive mole presenting with vaginal metastases often are cured by surgery, and it is also reported that secondaries in the vagina have disappeared without treatment. However, in a patient with a secondary in the vagina, appearing three months following hysterectomy, it is most unusual for the secondaries to disappear.

Methotrexate is an antagonist to folic acid, which is an essential substance in the formation of nucleic acid and especially desoxyribonucleic acid (D.N.A.).

Folic acid is essential for normal embryonal development and there has recently been reported the possibility of congenital abnormalities produced by its deficiency or its absence.

Lyndon Peer (1959) has found by animal experiments that, after the first week of development, a regular pattern of congenital abnormalities may be produced by critical stress—stress due to oxygen deprivation, X-ray exposure, vitamin deficiency, cortisone intoxication or virus infections. In the human we see rubella at 5 weeks resulting in cataract, and at 9 weeks resulting in congenital deafness, and recently another virus infection, Asian influenza, has been blamed in anencephaly on rather insufficient grounds (Pleydell, 1960).

It is an interesting fact that certain animals have a cleft lip as a constant anatomical formation, e.g., the hare.

Lyndon Peer (1958) repeated the work of Baxter and Fraser (1950) who subjected pregnant mice to injections of cortisone acetate between the 11th and 14th day of pregnancy; 85 per cent developed cleft palate. He then gave the vitamin B group separately—Riboflavin, Thiamine, Nicotinamide, B_{12}, Pantothenic Acid, Choline, Biotin and Inositol. All were ineffective, but, when vitamin B_6 was given together with the cortisone, the incidence was lowered to 45 per cent. When folic acid was given concomitantly with cortisone acetate, the incidence fell to 25 per cent and the simultaneous administration of folic acid and vitamin B_6 with cortisone, lowered it to almost zero.

Cortisone probably interferes with the functions of a given amount of vitamin B_6 and folic acid, and it is possible that some pregnant women, as a result of stress, secrete cortisone in amounts that inhibit the physiological functions of vitamin B_6 and folic acid—the two co-enzymes necessary for the normal development of the palatal processes. These patients have both co-enzymes in their diet, but evidently in not sufficient amounts. Conway (1958), speaking on the effect of supplemental vitamin therapy in limitation of cleft lip and palate, stated that heredity played the most important part in prevention, but he quoted a small series of cases which tended to show that the incidence of the abnormality can be lowered by supplemental vitamin therapy in the first trimester.

The unpleasant side-effects of Methotrexate therapy are said to be lessened by the simultaneous administration of the citrovorum factor.

The use of Methotrexate has not been as successful in teratoma and other testicular tumours—it appears to be effective in tumours of the female only.

Summary

(1) A case of chorionepithelioma is reported.

(2) The hysterectomy specimen was thought to be more likely an invasive mole than chorionepithelioma.

(3) A vaginal metastasis appeared 3 months after hysterectomy.

(4) Gonadotrophin titres, as reflected in urine tests on the toad, were at no stage high.

(5) The response to Methotrexate was remarkable.

(6) The toxic effects of the drug are described and the lessening of these effects by the simultaneous administration of the citrovorum factor is mentioned.

(7) The possibility of congenital abnormalities produced by folic acid deficiency is described.

I beg to thank Dr. Alison Garven, Pathologist at Footscray Hospital, for the pathological reports and Dr. Gerald Dunstan, Registrar, for obtaining supplies of Methotrexate through Lederle laboratories.

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A CASE OF METASTASIZING CHORIONEPITHELIOMA TREATED BY LOCAL EXCISION AND PITUITARY ABLATION WITH YTTRIUM 90

BY

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CANCERS of the breast and prostate are known to be hormone dependent and a large number of cases have now been treated either by excision of the gonads and adrenals or by pituitary ablation. A proportion of such cases, in some series 50 per cent of advanced breast cancers, respond and remain in remission for from one to two years and occasionally longer. The response to treatment by these means is not predictable at the present time.

Chorionepithelioma is a much more uncommon disease, but it seems reasonable to suppose that it might be a hormone dependent neoplasm and it is surprising to find so few cases treated by these measures reported in the literature. Luft *et al.* (1956) and Luft (1957) reported two cases of disseminated chorionepithelioma treated by hypophysectomy. In one of them the pulmonary metastases disappeared and the excretion of gonadotrophin in the urine fell to zero. This patient died subsequently while undergoing an operation for an arteriovenous aneurysm. Evans *et al.* (1959) reported a case of chorionepithelioma treated by pituitary ablation with yttrium 90. The pre-operative condition was critical and the patient died on the eighth post-operative day.

It seems justified therefore to report a further case of a metastasing chorionepithelioma treated by pituitary ablation with yttrium 90.

CASE REPORT

Mrs. I.S., a housewife aged 23 years, was admitted to hospital on 27th September, 1956. She gave a history of almost continuous slight vaginal bleeding since the normal delivery of her third child 4 months previously. For 3 weeks prior to admission she had noticed a non-tender lump in the vagina.

There was no relevant past obstetric, medical or family history.

On examination she was found to have a black nodule 2 cm. in diameter on the posterior vaginal wall close to the introitus and a smaller nodule on the anterior vaginal wall near the urethral meatus. The uterus was anteverted, soft and enlarged to the size of a 12-weeks pregnancy.

On 29th September, 1956 an examination under anaesthesia confirmed the findings. The cervical canal was dilated and placental like tissue removed from the uterine cavity and sent for histological examination. The section was reported as chorionepithelioma.

A photograph (Fig. 1) taken on 2nd October, 1956, shows the vaginal metastases which were rapidly increasing in size and number. On this date total hysterectomy and bilateral salpingo-oöphorectomy was performed. No peritoneal, omental or hepatic metastases were found. Section of the uterus showed that the tumour extended to the serosa but did not penetrate it (Fig. 2).

Microscopic examination of the tumour showed it to have the typical structure of a chorionepithelioma with well-marked syncytial cells, and composed mainly of large polygonal cells with clear cytoplasm corresponding to the cells of Langhans layer. There were numerous

mitotic figures and extensive areas of haemorrhage and necrosis. Tumour tissue was present in many venous sinuses in the muscle wall.

The post-operative recovery was satisfactory but the vaginal metastases continued to progress and broke down forming large necrotic ulcers (Fig. 3).

A post-operative chest X-ray showed numerous metastases in both lung fields.

A course of deep X-ray therapy to the pelvis was commenced but was discontinued after only 340 r. had been given and on 17th October the patient was transferred with a view to pituitary ablation with radioactive yttrium.

On 22nd October two radioactive yttrium rods were implanted into the pituitary.

The treatment was followed by rapid regression of the vaginal metastases (Figs. 4 and 5) and her general health improved considerably. She was allowed home, but on 8th December, 1956, having previously been quite well, she complained of headache and was flushed. She was re-admitted the following morning in the terminal stages of cardiovascular and respiratory failure, and died within a few minutes. Culture of the cerebrospinal fluid produced a pure growth of pneumococci and the cause of death was considered to be fulminating meningitis accentuated by cortisone insufficiency.

A subsequent post-mortem examination confirmed that death was due to a pyogenic pneumococcal meningitis. A careful search was made for metastatic chorionepithelioma. Multiple small deposits were found within the right lung, none larger than 1 cm. in diameter, while the left lung contained only a few deposits in the lower lobe. The vault of the vagina on the right side was puckered, the underlying tissues were thickened and indurated and a firm nodule 1 cm. in diameter lay between the vaginal vault and the overlying peritoneum. A raised indurated area extended up the anterior vaginal wall for 4 cm. the lower-most portion of which was ulcerated over an area of 0·5 cm. Nowhere else was any evidence found of secondary deposits, although all organs were carefully scrutinized and sections examined histologically.

Multiple sections were taken from suspected areas in the vagina and lungs. Most showed an appearance of haemorrhage and necrosis bordered by subacute and acute inflammatory cells. In 3 sections only were malignant cells seen; two of these were from lung nodules and showed small groups of malignant cells in the boundary zones of necrotic areas. They consisted of large pleomorphic hyperchromatic cells with scanty cytoplasm and many of the nuclei showed evidence of karyolysis and karyorrhexis. The remaining section in which malignant cells were seen was from the vaginal vault. The cells were few in number and had hyperchromatic irregular nuclei and scanty cytoplasm.

It was considered that almost complete necrosis of the metastases had occurred both locally and in the lungs.

Sections of the pituitary showed only a rim of normal tissue intact at one edge; almost the whole gland having undergone necrosis.

Discussion

In this case remission of the disease occurred very soon after pituitary ablation, the rapid disappearance of the vaginal metastases being a particularly striking feature. However, it must be remembered that the natural history of chorionepithelioma is unpredictable. The great majority of cases with widespread dissemination go progressively and rapidly downhill, but several authors have reported the spontaneous disappearance of metastases. Brews (1939) reported on the spontaneous resolution of a vaginal metastasis from a chorionepithelioma which developed soon after normal labour. The metastasis disappeared within 14 days of hysterectomy and the patient was alive and well 11 years later (Brews, 1950). More recently, Perlson and Whitsitt (1960) reported a case of chorionepithelioma with multiple metastases, all of which underwent spontaneous regression after local pelvic surgery. The patient was still in remission 39 months later. There are many similar reports in the literature and, although some may be the result of misdiagnosis, many are well authenticated. It has been suggested that this unexpected behaviour may be due to the formation of anti-tumour antibodies.

Nevertheless the remission of the disease both

in the case described above and in that reported by Luft *et al.* (1956), occurring so soon after ablation of the pituitary, at least suggests that this procedure may have been responsible.

The risks of pituitary ablation whether by surgical removal or radioactive implant are not negligible but seem amply justified in cases where the expectation of life in the absence of treatment is a few months at most. The development of a fatal meningitis such as occurred in this case, after implantation of the pituitary with a radioactive substance by the trans-sphenoidal route, is a recognized but not unduly common complication. Greening (1956) reported a series of 50 pituitary ablations with radioactive gold *via* this route with no mortality and no case of cerebrospinal fluid rhinorrhoea or meningitis. Ironside and Moseley (1958) had two cases of meningitis, one of which was fatal in a series of 26 cases using yttrium 90.

Recently chorionepithelioma has been successfully treated with cytotoxic drugs. This was first practised in America by Hertz and his colleagues (1958) using the folic acid antagonist methotrexate. In this country Bagshawe and McDonald (1960) have used combinations of methotrexate, 6-mercaptopurine and chlorambucil with considerable success. It may be that both cytotoxic agents and pituitary ablation will find a place in the treatment of metastasizing chorionepithelioma; pituitary ablation being kept in reserve until cytotoxic agents have been tried.

Summary

A case of a metastasizing chorionepithelioma treated with local pelvic surgery and pituitary ablation with yttrium 90 is reported.

The possible place of this form of treatment in the management of these tumours in the future is discussed.

I wish to thank Mr. C. M. Gwillim, under whose care the patient was admitted to the Samaritan Hospital for Women, for permission to publish this case, and for his help and encouragement. My thanks are also due to Mr. W. P. Greening, who carried out the pituitary ablation at the Royal Marsden Hospital, for permission to publish.

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FIG. 1
Vaginal metastases just prior to hysterectomy.

FIG. 2
Uterus showing the chorionepithelioma.

FIG. 3
Breaking down vaginal metastases just prior to pituitary ablation.

FIG. 4
Vaginal metastases ten days after pituitary ablation. Rapid regression is evident.

FIG. 5
Almost complete disappearance of vaginal metastases four weeks after pituitary ablation.

OLIGURIA CAUSED BY THE TRANSFERENCE OF FOETAL BLOOD INTO THE MATERNAL CIRCULATION

BY

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THE transference of foetal blood into the mother's circulation in relatively large quantities, appears to be a rare phenomenon. The first case of proven transference of the foetal blood into the maternal circulation due to an obstetric manœuvre was recorded by Chown (1954, 1955), although the possibility of this occurrence had been appreciated by Wiener (1948). The consequences to the mother in the case reported by Chown were not grave, although clinically she suffered from a mismatched transfusion reaction. The child, however, died.

Since Chown's case paediatricians have tested maternal blood for foetal red cells in the case of newborn babies found to be suffering from anaemia of unknown aetiology, and upon several occasions it has been found that foetal red cells have indeed gained access to the maternal circulation. The quantity of blood transferred has usually been thought to be small, and the mothers have not been affected clinically (Gunson, 1957; O'Connor, Shields, Kohl and Sussman, 1957a, 1957b; Shiller, 1957; Goodall, Graham, Miller and Cameron, 1958; Zipursky, Hull, White and Israels, 1959).

The case now reported is the second on record where the transference of foetal blood to the maternal circulation was in sufficient amount to cause the death of the baby, and grave consequence to the mother. This case is one of rupture of the placental barrier by gross trauma.

RECORD

The patient was a young woman expecting her fourth child in two weeks time. It was Monday morning, 2nd February, 1955 and she was pegging out her laundry on a clothes line, standing on a kitchen chair. She tumbled over, and apparently some part of the chair dug into her abdomen, for the skin in one area showed a bruise. A few minutes after this accident, she was found "writhing in agony on the ground", and she was brought into hospital where she arrived within 40 minutes.

On arrival the patient was in a distressed condition and was very restless because of the pain referred to the bruised area on the abdomen, but there was no evidence of blood loss, revealed nor concealed, at this stage, and the blood pressure was 110/80.

The foetal heart was not heard, however, and yet the mother had felt foetal movements during the morning before the accident had occurred.

Soon after admission she was given 100 mg. of Pethidine because of the pain, and it was noted that the uterus was contracting. Labour progressed uneventfully. Blood examination of the mother showed that she belonged to group O Rh+ blood group. The only unusual feature of the case was the distress and discomfort caused to the mother by the contraction of the uterus, and Pethidine did not have a very satisfactory effect. Spontaneous delivery occurred of a stillborn female child three hours after admission, and the third stage was normal. There was, however, a 14-ounce blood loss following the placenta, and this could have been the result of a small concealed accidental haemorrhage.

Two hours after delivery, she was catheterized

and 2 ounces of dark blood-stained urine were obtained, and during the next 18 hours, despite a normal blood pressure, only a further 1¼ ounces of urine were excreted.

On the second day of the puerperium, her blood urea was found to be raised, and treatment for oliguria was commenced.

The figures (Figs. 1, 2, 3, 4) show the course of events from now on, and record of fluid intake and output, the changes in the blood electrolytes, sodium potassium, chlorides, blood urea, and the alkali reserve. These are all shown expressed both as milligrammes per cent and milli equivalents per litre. These pictures show the course that the oliguria took. Happily she responded to treatment and recovered.

It now became of considerable interest to try to discover why the patient suffered from oliguria, and why the child had died, for it was known to be alive on the morning of the accident. The degree of trauma did not suggest that a "crush syndrome" type of pathology was present. There was no indication of toxaemia of pregnancy, and, as far as we could tell, she had never suffered from a low blood pressure caused by shock, certainly not of sufficient depth nor duration to cause oliguria, nor the death of the child. (The patient was in hospital within 40 minutes of the accident, and, on her arrival there, her blood pressure was found to be normal.)

Autopsy of the child revealed no obvious abnormality. Apparently we had checked and re-checked every system, and still the problem

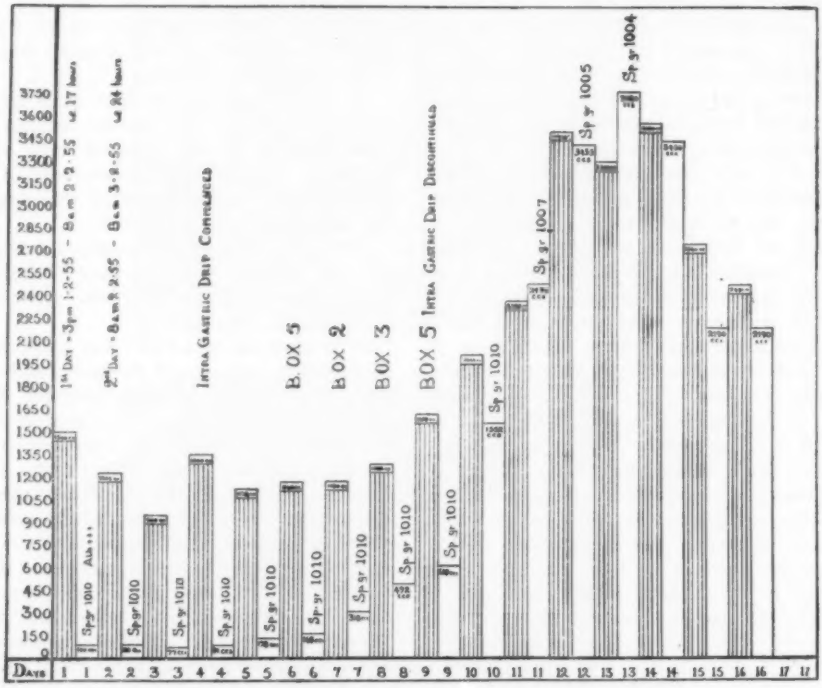
1st Day - 3pm 1-2-55 - 8 a.m 2-2-55 = 17 hours
2nd Day - 8 a.m 2-2-55 - 8 a.m 3-2-55 = 24 hours
Intra Gastric Drip Commenced
BOX 5
BOX 2
BOX 3
BOX 5 Intra Gastric Drip Discontinued
Sp gr 1010
Sp gr 1007
Sp gr 1005
Sp gr 1004
Days

FIG. 1

This shows the fluid intake and urinary output during the illness.

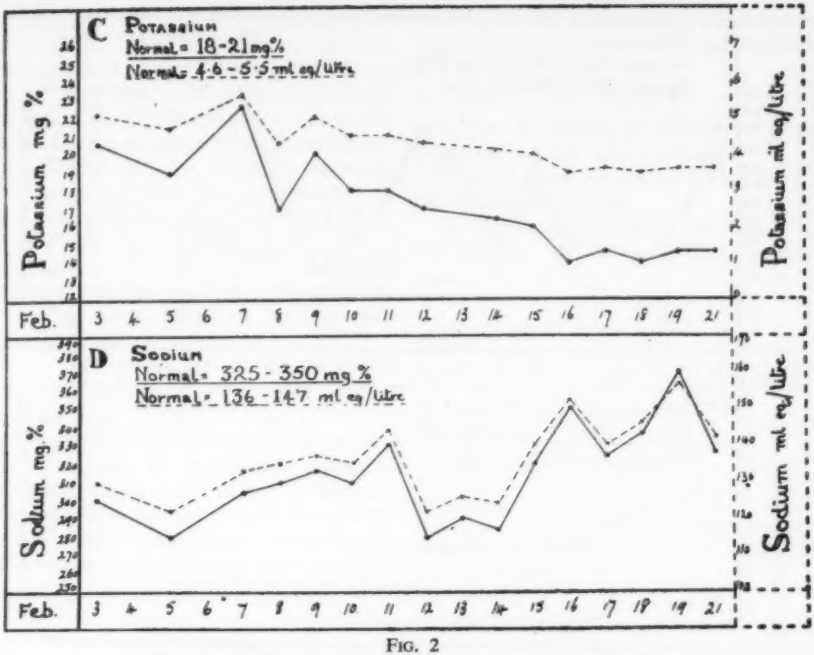

FIG. 2

Charts of the blood sodium and potassium content during the illness.
The continuous line = expression in mg./per cent.
The interrupted line = expression in ml. eq./litre.

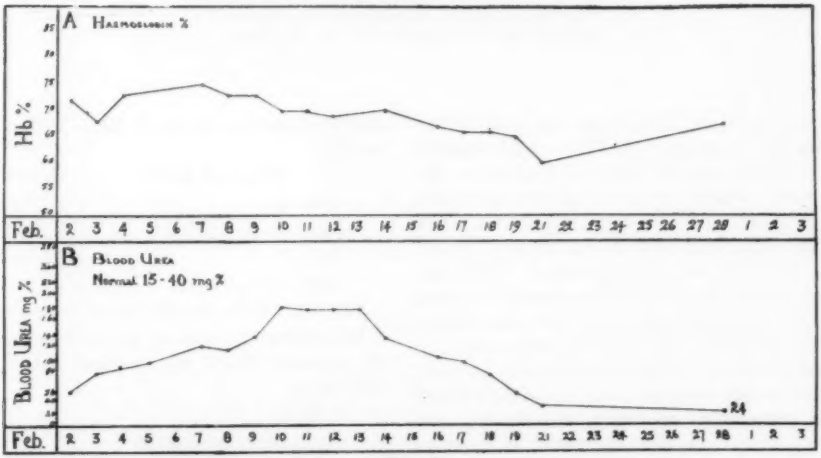

FIG. 3

Shows the haemoglobin and blood urea levels during the illness.

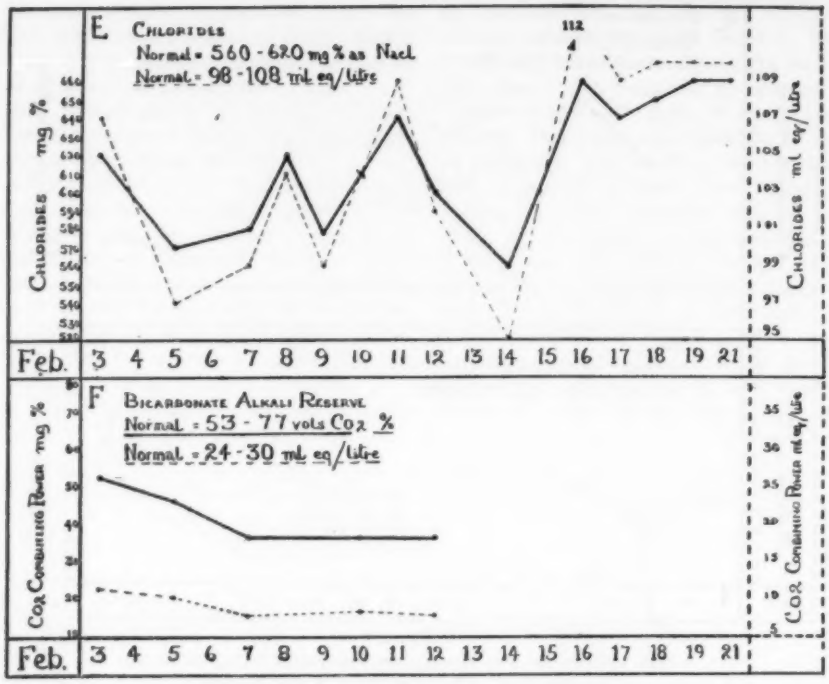
E. Chlorides
Normal = 560 - 620 mg % as Nacl
Normal = 98 - 108 ml eq/litre
Chlorides mg %
Chlorides ml eq/litre
112
Feb. 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 21
F Bicarbonate Alkali Reserve
Normal = 53 - 77 vols Co2 %
Normal = 24 - 30 ml eq/litre
Co2 Combining Power mg %
Co2 Combining Power ml eq/litre
Feb. 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 21

Fig. 4

Shows the blood chloride and alkali reserve readings.
Continuous line = expression in mg./per cent.
Broken line = expression in ml. eq./litre.

remained unsolved. There was no evidence of intracranial damage, and the child seemed normal in all respects, and yet looking at the body there recurred to the mind that there was something unusual about its appearance—and suddenly what had eluded one became crystal clear—the child was exsanguinated. What had happened to its blood? Had the trauma occurred over the placental side, and had the foetal-maternal placental barrier been ruptured?

With the object of trying to discover whether this had in fact occurred, and the child's blood passed into the mother's circulation, the mother's blood was now examined in terms of alpha and beta agglutinin titres. (It was known that her blood was group O Rh+ whereas the child's blood was group B Rh+.) Here are the results:

Maternal Blood	*Controls*
Anti A	(1) 1 in 128
Agglutinin 1 in 256	(2) 1 in 256
Anti B	(1) 1 in 64
Agglutinin 1 in 64	(2) 1 in 64

This was on the second day of the puerperium.

Dramatically, however, by the 14th day, when the maternal blood was re-examined, the titres were now:

Anti A
Agglutinin, no change
Anti B
Agglutinin 1 in 8,000

It seemed, therefore, that a considerable quantity of child's blood had been sucked into the maternal blood stream, the quantity being sufficient to give rise to these haematological findings, and so the oliguria might be due to the equivalent of a mismatched blood transfusion. Since the bruise on the mother's anterior abdominal wall was over the right fundus of the uterus, and since the child was in the L.O.A. position, it seems very probable that the injury occurred over the placental insertion, rupturing the placental barrier, and so allowing the transference of foetal blood to the maternal circulation to occur.

Conclusion

Since foetal blood has gained access to the maternal circulation in considerable quantity in both Chown's case and this one, in circumstances of trauma to the placenta, the possibility arises of a similar transference occurring in cases of abruptio placentae, and it is possible that herein lies the aetiology of cases of anuria sometimes associated with this condition.

Summary

A case is reported of abdominal injury in a pregnant woman with the result:

(1) Foetal death for no obvious reason.

(2) Maternal oliguria.

An explanation of these findings is offered, and this is supported by the haematology of the case.

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GENITAL TRACT PAPILLOMAS WITH PREGNANCY

Review of Literature and a Case Report

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PAPILLOMA is a neoplastic growth, with tree-like branching processes. To describe it in Marsh's (1952) words it is "A benign epithelial neoplasm usually composed of pavement epithelium with supporting connective tissue core and frequently papillary in nature". A histologically similar lesion in the genitalia is condyloma acuminatum. An attempt has been made to distinguish it from papilloma microscopically but the difference is so insignificant that only clinical differentiation is used. When the cervix alone is involved the lesion is known as papilloma but when it is multiple involving the cervix, vagina and vulva it is termed condylomata acuminata.

Condylomata acuminata, also known as venereal warts, are due to virus infection. They were originally thought to be associated with venereal diseases and hence acquired the name of venereal warts. Kistner and Hertig (1955) have reported a case where the patient's husband had a similar lesion in the genitalia. Condyloma acuminata grow rapidly during pregnancy and the whole vagina may be filled up with a fungating growth. The growth regresses postnatally, but does not disappear completely on its own.

RELATIONSHIP OF PAPILLOMA TO PREGNANCY AND MALIGNANCY

The relationship of papillomas to malignancy has been studied in detail. A few of Green and Peckham's (1954) cases showed basal cell hyperplasia and 4 were associated with preinvasive carcinoma and in one the lesion persisted and behaved as frankly malignant and killed the patient. These authors believe that the relationship is coincidental. Kistner and Hertig (1955) in a review of 68 cases, found 4 definitely malignant but all these were in the older age group. They consider the growth in non-pregnant and post-menopausal women as a separate entity from the one associated with pregnancy. Kistner and Hertig (1955) have described the cervical papillomas associated with pregnancy as "Cock's Comb Polyp". They had 4 such cases, all under 27 years of age and, in all, spontaneous regression occurred during the puerperium. The tendency of papillomas to disappear is apparently not limited to pregnant patients. Disappearance of papillomas in non-pregnant women has been reported by Green and Peckham (1954). On the other hand not all of them disappear. In fact

in one of Green and Peckham's cases papillomatosis continued and extended to the endocervix and endometrium. In another patient an apparently benign growth became invasive as it progressed. At other times coincidental malignant lesions are present and persist even after the papillomas have regressed.

Marsh believes that the relationship between papillomas and pregnancy is very dubious since pregnancy is so frequent and papillomas so rare. In his 31 cases 16 were pregnant. Green and Peckham believe that the apparently higher incidence in pregnancy is due to the fact that pregnant patients are carefully examined. Eleven of their patients from Chicago maternity centres were naturally all pregnant but only 4 out of 15 who did not come from maternity centres were pregnant. On the whole it is apparent from the study of the literature, that, when associated with pregnancy, papillomas are mostly benign and often disappear during the puerperium but are likely to recur in a succeeding pregnancy.

Genital papilloma is rare. Kistner and Hertig (1955) in a study of 40,000 cervical biopsies over a period of 20 years found only 17 cases either of condyloma acuminatum or papilloma. From 6,500 biopsies from the Boston Lying-in Hospital over the same period, they found only 4 cases of papilloma. A survey of the literature shows that only 84 cases have been reported, and in almost all of them the cervix was involved alone or along with the vulva and vagina. On an exhaustive search of the literature no report could be traced, where the cervix was entirely free from the growth as in the case which is reported below.

Case Report

Mrs. S.K., aged 27 years, married 10 years, para-5, was first seen in the out-patient department on 2nd November, 1959, with a history of amenorrhoea of 1¾ months duration, followed by blood-stained discharge for 2½ months. Her last menstrual period was on 5th July, 1959. She started bleeding *per vaginam* on 25th August, which lasted for only one day, and was moderate in amount. Bleeding stopped for two days and was followed by blood-stained foul-smelling discharge which was pink, yellow or white. Five weeks later she started bleeding *per vaginam*, moderate in amount soaking two to three pads a day and the discharge was still foul-smelling. This had continued for a month prior to her visit to the hospital. Before the present complaint her periods were regular with normal flow. She had no other complaints of pain or fever. She had been getting penicillin injections for about a week before her visit. The patient had had one premature and four full-term normal deliveries. Three daughters and one son were alive and well. The last delivery was 1¾ years previously. Her second pregnancy ended in premature delivery at 8 months, and the child died on the first day. She had had no abortions.

On Examination

She was a young woman of average build. She looked slightly anaemic. Her blood pressure was 110/80. The temperature was normal, the pulse 80 per minute. The cardiovascular and respiratory systems were normal. On abdominal examination the uterus was found to be enlarged to the size of about 16-weeks pregnancy. The liver and spleen were not palpable. On inspection of the external genitalia a small papillary growth about 1 cm. in diameter was seen at the vaginal orifice on the right side. Blood-stained discharge was present. On bimanual examination a papillomatous growth about 6 cm. in diameter was found to be arising from the right side of the vaginal vault. The cervix was free of growth and was pushed to the left side. The uterus was of the size of 16-weeks pregnancy and was soft. On speculum examination a papillomatous growth was seen almost filling the vagina and arising from the right side, and there were areas of necrosis in places. It was friable and bled on touch. A small piece of growth came off during examination and on histopathological examination showed squamous papilloma with no evidence of malignancy (59-879). The patient was admitted on 11th November, 1959.

Pathological Investigations

Blood: Hb. 9·56 g. per cent. Total red blood count 4·30 millions/c.mm. Total white blood count 11,000 c.mm., polymorphs 70 per cent, lymphocytes 24 per cent, monocytes 6 per cent. The blood picture showed normocytic slightly hypochromic anaemia. E.S.R. 24 min. Westergren. Blood urea 25 mg. per cent. Blood group AB. Kahn test: negative. Urine was normal.

She was given Multivite and iron tablets and a high protein diet. Dequadin (Dequalinium 10 mg.) pessaries were inserted in the vagina one every night for one week. She was given two transfusions of blood of AB group and each 350 ml., to obtain a quick rise of haemoglobin which came up to 11·5 g. by the 16th November, 1959.

Abdominal hysterotomy, sterilization and a repeat biopsy of the growth was done on 19th November, 1959.

Hysterotomy was performed first. The foetus was of the size of 18-weeks gestation; the placenta appeared rather large, pale and oedematous. Sterilization was done by Pomeroy's technique.

On vaginal examination after hysterotomy, it was found that the vaginal growth was about 1½ times the size as seen 2 weeks earlier. There were multiple new growths present on the vulva on both sides of the

vaginal orifice. A growth of about 1½ cm. × 1 cm. had appeared on the anus at the 2 o'clock position (Fig. 1). Anal and a few vulval growths were excised and bleeding was controlled with mattress sutures. A bit of the growth from the vagina was excised for histopathology.

Histopathology

59-962—Condyloma acuminatum of vulva, vagina and anus (Figs. 2 and 3). 59-975—Placenta within normal limits. 59-1013—An autopsy on foetus was performed. The thyroid, adrenal, lung, liver, spleen and kidney were found to be grossly as well as microscopically within normal limits.

Post-operatively patient was given achromycin 250 mg., 6-hourly, for 8 days. The immediate post-operative period was uneventful, but she had a rise of temperature 12 days after the operation, maximum rise being 103° F. A high vaginal swab was taken and she was put on strepto-penicillin (streptomycin ½ g. plus penicillin 400,000 units). The high vaginal swab culture showed *Staphylococcus albus*, coagulase negative, sensitive to only polymyxin and resistant to strepto-penicillin, aureo-, achro-, chloro- and terramycin. Temperature settled down after 3 days and the discharge gradually diminished in amount. The culture report was ignored as the patient was already improving. Strepto-penicillin was discontinued after 5 days. Examination on 6th December, 1959 (on 17th post-operative day) revealed a bulky uterus. The papillomatous growth was much smaller, hardly a quarter of its original size. On speculum examination, darkish bleeding was present at the cervical os. On re-examination on 12th December, 1959 (on 23rd post-operative day) the uterus was in upright position, slightly bulky. The vaginal growth had completely disappeared and vaginal vault felt smooth and normal. On speculum examination only two tiny pink spots could be seen on the right side, one an inch below the cervix and another about an inch above the introitus. Her general condition was good and the haemoglobin was 12·5 g. On 15th December, 1959, no trace of growth could be seen and she was discharged.

Follow-up

The patient was seen on 15th January, 1960. She was doing well. She had a menstrual period on 29th December, 1959. Pelvic examination revealed no trace of papillomas. The uterus was normal size and in good position.

Speculum examination revealed healthy cervix and vagina with no trace of papillomas.

Discussion

According to the definitions in the literature, this case on account of the multiplicity of lesions could only be put down as one of condylomata acuminata though that diagnosis cannot be fully justified. Condylomata acuminata are supposed to occur in patients with unclean habits and do not regress after delivery This patient was intelligent and educated. She came from a good family and the lesion disappeared completely within four weeks of the termination of pregnancy.

Papillomas occurring during pregnancy have often baffled obstetricians and sometimes the pathologists as well. It happened in Martin and Kenny's (1950) case where recurrence with exuberant growth took place in the succeeding pregnancy and Caesarean hysterectomy was resorted to. In Adrian Hill's (1948) case, malignancy was suspected due to the rapidity of the growth and the vascularity, in spite of the doubtful histological report. Caesarean section was done, and radiation therapy was contemplated. However, the latter was not required as the growth disappeared postnatally and the benign nature of the lesion was thus established. Edmondson, Levi, Evans and Horn (1945) reported 6 cases of papilloma of the cervix. In one of their cases radium was used 9 days post-partum because the lesion was grossly thought to be carcinoma. Microscopically however it was a typical papilloma. The papillomatous structure might temporarily mask the malignant characteristics of co-existing carcinoma; on the other hand a papilloma from its hyper-activity may be mistaken for a cervical cancer and improper treatment be thus instituted. The patient presented us with a problem, as the growth was increasing rapidly and there was continuous bleeding as well as offensive discharge. Local excision of such an extensive and vascular growth during pregnancy was not considered to be without hazard. There were chances of recurrence as she was only 16-weeks pregnant and had a long way to go. Hysterotomy, combined with sterilization, in this case was considered as the treatment of choice, in view of the reported recurrences and potential malignancy. Fortunately she was only too keen to stop further child-bearing. Only biopsies were taken at the time of hysterotomy and it was felt that, should the papillomas persist, excision could be done later, when vascularity would be reduced. However due to spontaneous disappearance postnatally, no further treatment was required. In fact, the recovery was dramatic,

FIG. 2
Photomicrograph of papilloma. ×31.

FIG. 1
A—Vaginal papilloma.
B—Vulvar papilloma.
C—Anal papilloma.

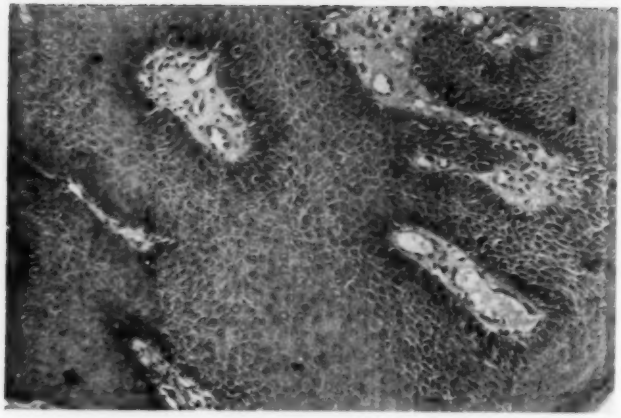

FIG. 3
Photomicrograph of papilloma 59-962. ×104.

specially since she was referred by her doctor with the mistaken clinical diagnosis of carcinoma of vagina with pregnancy and was warned of the poor prognosis.

Summary

(1) An unusual case of pregnancy with multiple papillomas of vagina, vulva and perineum and not involving the cervix is presented.

(2) The literature on the subject is reviewed.

(3) The obstetrician's problem in managing such cases is discussed.

Acknowledgments

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BRENNER TUMOURS OF THE OVARY

A Clinico-pathological Study

BY

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BRENNER tumours of the ovary have caused a great deal of interest since they were first recognized as an entity. Credit for this has been given to Brenner (1907) although several reports of similar tumours had been made before Brenner's description of 3 cases (Macnaughton Jones, 1898; Orthmann, 1899; Fothergill, 1902; Hellier and Smith, 1902). Most reports have been concerned with the histogenesis of these tumours and a great volume of literature has accumulated on the subject. They were originally thought to arise from follicular cells—"oophoroma folliculare" (Brenner); "folliculoma ovarii" (Ingier, 1907); "egg-like cells in solid ovarian tumours" (Fothergill), but Meyer (1932) drew attention to the similarity of these tumours to the Walthard nests found in the cortex of some ovaries, and this has been accepted by most authors as the source of origin of these tumours. Schiller (1936, 1940) suggested that some Brenner tumours might arise by "dislocation" into the ovary of germ cells which primarily belonged to the urinary system, while Greene (1952) thought that they might have several modes of origin, including the ovarian stroma, the rete ovarii (as suggested by Schiller) and the surface epithelium. The tumours arising from the surface epithelium in the early stages "resemble or in reality may be nothing more than the so-called 'Walthard bodies' of the ovary" (Greene, 1952). Neiman (1936) also postulated an origin from the ovarian stroma according to the theory of Fischel (1932). More recently, other authors have supported this theory for some Brenner tumours, particularly with reference to the fibromatous part of the tumours (Biggart and Macafee, 1955; Ince and Salm, 1959) and there seems to be increasing agreement that the fibrous tissue is an integral part of the tumours and not a reaction to the epithelial islands (Teoh, 1953). Biggart and Macafee consider that the stroma "may undergo the same sequence of events as is seen in the thecoma-fibroma series of tumour". It is of interest in this connexion that some authors report an association between Brenner tumours and endometrial hyperplasia (Mackinlay, 1956; Eton and Parker, 1958), suggesting that these tumours might have hormonal effects, in contrast to the view commonly accepted that they are without hormonal influence (Novak and Novak, 1958).

Many of the previous reports have not included the appearance of the endometrium, and in view of the rare nature of these tumours, it was felt that the reporting of 30 new cases, many with endometrial findings, would be of importance.

MATERIAL

Fifty-one thousand three hundred and twenty surgical specimens have been examined in this hospital in the past 25 years (1935–1959), and during this time 31 Brenner tumours from 30 patients have been discovered. Blocks and slides from 30 of these tumours have been available for examination together with the blocks of the endometrium from 19 of the patients. Sections were cut at 4μ and stained with haemotoxylin and eosin in the routine manner. Unfortunately no material was available for frozen section so fat stains were not possible.

History

A history was available in 28 cases. The ages varied from 30–76 years, 19 of the patients being in the age group 40–59 years. Twelve of the women were post-menopausal and 16 were pre-menopausal. The main symptoms may be summarized as follows:

Abdominal pain	18
Abnormal vaginal bleeding (post-menopausal, 5; menorrhagia and metrorrhagia, 11)	16
Abdominal swelling	7
Fullness of breasts	2
Backache	2
Stress incontinence	2
Dyspareunia	2
Sterility	1

Tumour Pathology

Twenty-five of the tumours were solid, while 6 of the tumours occurred in the walls of cysts—5 of the cysts were of the pseudomucinous cystadenomatous variety, the other cyst being a serous cystadenoma.

The Brenner tumours varied in size from large fibroma-like tumours which filled the pelvis, to microscopic seedling tumours. Of the latter, approximately half seemed to arise from the ovarian cortex and half from the hilum.

The tumours varied greatly in the proportion of epithelial islands to fibromatous stroma.

Epithelial Islands. The cells making up these islands were squamous in appearance but without demonstrable intercellular bridges. The cytoplasm was clear or faintly granular. The nuclei were central, round or oval, many showing the classical grooved appearance. In some tumours the epithelial cells seemed to fade off into the surrounding stroma (Fig. 1), whereas in other tumours the surrounding stroma was compressed to form a pseudocapsule to the island (Fig. 2). Many of the islands showed areas of cystic change. These varied from small spaces filled with mucinous material, to larger spaces which occupied almost the whole of the island (Fig. 3). The spaces were usually lined by flattened cells, but occasionally they showed columnar cells resembling those found in pseudomucinous cystadenomata (Fig. 4). No Call-Exner bodies were seen.

Fibrous Stroma. In some tumours the stroma was cellular, with plump, oval nuclei resembling theca interna cells. There were all gradations between these and a hyaline stroma with areas of calcification. In several tumours, the hyaline change was most noticeable as a narrow rim surrounding the epithelial island. The stroma was made up of interlacing bundles of fibrous tissue but in some tumours it was so arranged that it gave the appearance of a circular coat surrounding the epithelial island (Fig. 5).

No mitotic activity was seen either in the epithelial islands or in the stroma.

Endometrial Changes

The endometrium was available for examination in 5 of the post-menopausal women. Two showed a senile atrophic endometrium, 2 a senile cystic endometrium (in 1 of these cases the endometrium was polypoidal), and the fifth case showed non-secreting cystic hyperplasia (Fig. 6). This woman, age 65, complained of post-menopausal bleeding, and was found to have a Brenner tumour, 7·5 cm. in diameter, replacing the left ovary.

Of the 16 pre-menopausal women, the endometrium was examined in 13. Four showed a regenerative pattern endometrium corresponding to the first half of the menstrual cycle. In 5 the endometrium was secretory and in 2 of these it was hyperplastic, although the secretory activity was poor in one case and the glands were cystic, suggestive of the "Swiss-cheese" type of hyperplasia. Three cases showed non-secreting hyperplasia; one of these cases also had endometriosis affecting both ovaries, another had a small follicular cyst and the third had a thecoma (Fig. 7) in one ovary and a Brenner tumour (Fig. 5) in the other. The endometrium in this case (Fig. 8) was grossly thickened and there was an endometrial polyp 4 cm. long.

In the remaining case an endometrial adenocarcinoma (Fig. 9) was present associated with bilateral Brenner tumours, wherein the epithelial elements were considerably more glandular than

is normal, the epithelium often being reduced to a narrow rim of flattened cells (Figs. 10 and 11). The stroma showed moderate hyaline change. Best's carmine stain revealed small quantities of glycogen in the epithelial islands; mucicarmine and periodic acid–Schiff stains were positive for mucin. No evidence of malignancy was present in either ovary.

The endometrium in one of the 2 cases in which no history was available showed a secretory pattern, but there were areas in the endometrium where the glands were non-secretory and cystic.

Associated Tumours

Thirteen cases had ovarian cysts of varying sizes. Of these:

4 were pseudomucinous cystadenomata.
1 pseudomucinous cystadenocarcinoma.
4 serous cystadenomata.
2 follicular cysts.
1 dermoid cyst.
1 endometrial cyst.

In the 5 pseudomucinous cysts and in 1 serous cyst, the Brenner tumour occurred in the wall of the cysts. The Brenner tumour occurred as a solid tumour in the same ovary as the endometrial cyst. One other case showed ovarian endometriosis and, in this case, areas of endometriosis occurred both in the substance of the ovary and in the Brenner tumour.

One case was associated with a thecoma in the opposite ovary. Uterine fibromyomata occurred in 6 cases and an adenocarcinoma of the body of the uterus was present in the case with bilateral Brenner tumours.

Discussion

The possibility that Brenner tumours might have an endocrine effect has aroused interest in recent years. The view expressed by Novak and Novak (1958) that these tumours do not have any hormonal influence is the one generally accepted. Many reports of vaginal bleeding in association with Brenner tumours have been recorded, but this bleeding has usually been attributed to factors other than Brenner tumours (Novak and Jones, 1939; Jondahl *et al.*, 1950). More recently attention has been drawn to the similarity of the stroma in Brenner tumours to that in thecomata and the finding of refractile fat (Biggart and Macafee, 1955) in some tumours has made this similarity even greater. Abnormal uterine bleeding has been present in over 25 per cent of cases in several series and endometrial hyperplasia in approximately 10 per cent (Morris and Scully, 1958). Mackinlay (1956) and Eton and Parker (1958) report several cases of vaginal bleeding associated with Brenner tumours and mention many more cases from the literature. These tumours might be associated with oestrogen production but proof is difficult as so many of the previous records have not included details of the endometrium.

Shaaban, Abdine and Youssef (1960) report a case of a post-menopausal woman on whom oestrogen estimations were performed 5 weeks after removal of a Brenner tumour which was associated with an endometrial adenocarcinoma. They found greatly elevated levels of oestrogen excretion.

In the present series 16 of 28 cases presented with abnormal vaginal bleeding and the endometrium was available for study in 12 of these cases. One patient had an endometrial adenocarcinoma and there was evidence of endometrial hyperplasia in 6 other cases. Four of these showed non-secretory hyperplasia such as might follow oestrogen stimulation, but 1 of these cases also had a thecoma and another case had a follicular cyst. Thus only 3 cases showed endometrial changes which might be attributed to oestrogen production by the Brenner tumour.

Endometrial adenocarcinoma has been found on several occasions in association with Brenner tumours (TeLinde, 1930; Dockerty and MacCarthy, 1939; Reagan, 1950; Teoh, 1953; Mackinlay, 1956; Eton and Parker, 1958) and in some of these cases there was evidence of preceding cystic glandular hyperplasia of the endometrium. Other authors (Schiffmann, 1932) have noted the association of cystic glandular hyperplasia with Brenner tumours, although Novak and Novak (1958) dismiss this on the grounds that cystic hyperplasia might be found without any ovarian tumour. Biggart and Macafee (1955), however, think that it is the thecal component of Brenner tumours which

FIG. 1

Brenner tumour. The epithelial island fades into the stroma. ×110.

FIG. 2

Brenner tumour. The stroma is cellular and compressed around the epithelial island to form a pseudo-capsule. ×125.

FIG. 3

Brenner tumour. The epithelial island shows gross cystic change. ×110.

FIG. 4

Brenner tumour. The cystic spaces in the epithelial islands are lined by columnar cells resembling pseudomucinous epithelium. ×346.

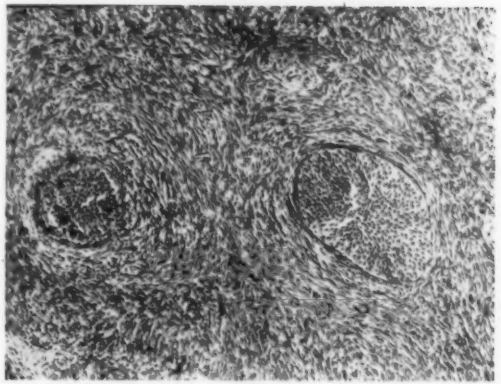

FIG. 5

Brenner tumour with cellular stroma arranged in a circular manner about the epithelial islands. ×70.

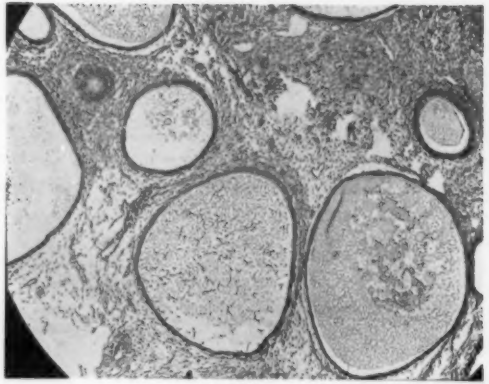

FIG. 6

Endometrium. Gross cystic hyperplasia associated with an ovarian Brenner tumour. ×86.

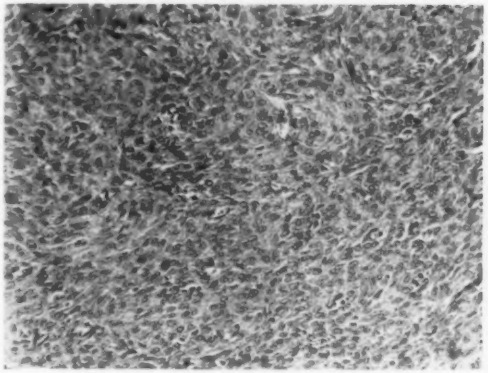

FIG. 7

Ovarian thecoma. ×87.

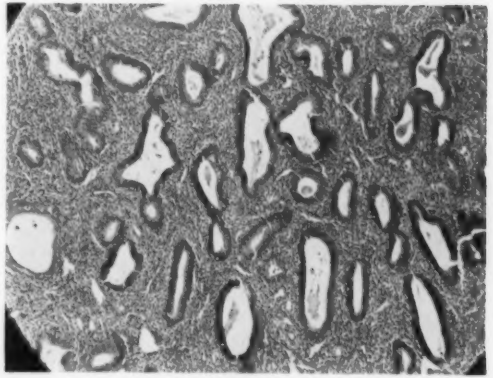

FIG. 8

Endometrium. Non-secretory cystic hyperplasia associated with a Brenner tumour (Fig. 5) and a thecoma (Fig. 7). ×43.

with a Brenner tumour (Fig. 5) and a thecoma (Fig. 7). ×43.

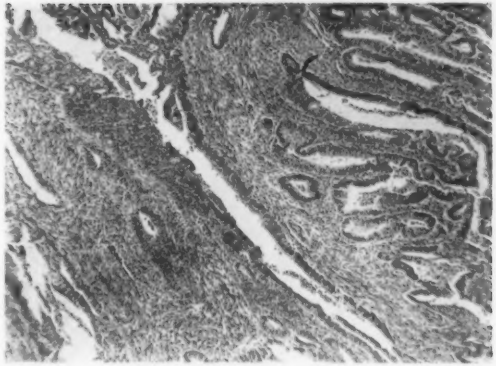

FIG. 9

Endometrium. Invasive adenocarcinoma associated with bilateral Brenner tumours (Figs. 10 and 11). ×37.

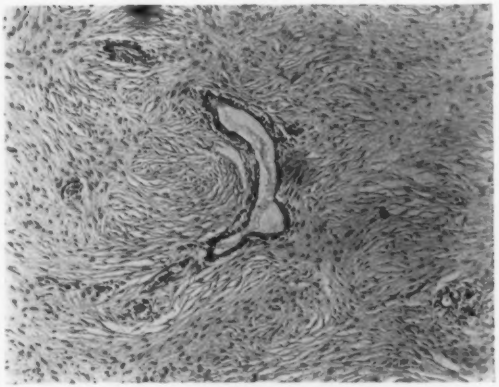

FIG. 10

Left ovary. Brenner tumour with epithelial islands reduced to a cystic space surrounded by a single layer of cells. Hyaline change in stroma. ×70.

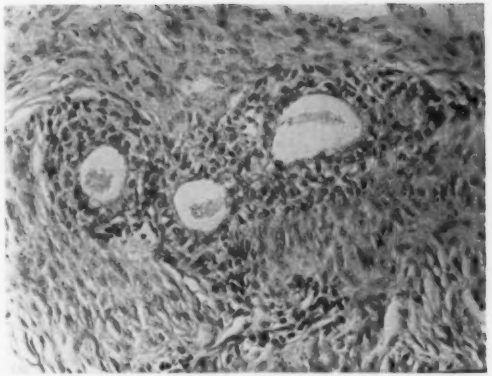

FIG. 11

Right ovary. Brenner tumour. Cellular epithelial islands and stroma. Other areas of this tumour resembled Figure 10. ×87.

accounts for the endometrial changes in these cases. In this series the presence of a senile atrophic endometrium was accompanied by a hyaline, and often calcified stroma in the Brenner tumours, but in those cases showing endometrial hyperplasia the cellularity of the stroma varied considerably and did not appear to be closely related to the degree of hyperplasia. The stroma in the Brenner tumours associated with the endometrial adenocarcinoma was only moderately cellular and the epithelial islands in this case were reduced to small cysts lined by one or two layers of cells (Fig. 10).

Three other patients presented interesting features possibly related to oestrogen stimulation. Two women complained of fullness and "tingling" in their breasts. One woman stated that she also had sickness of such severity that she thought she was pregnant (although she had post-menopausal amenorrhoea for 2 years). At laparotomy this woman was found to have an ovarian dermoid cyst as well as a Brenner tumour. The other woman had a follicular cyst as well as a Brenner tumour. Post-menopausal enlargement and tenderness of the breasts in association with Brenner tumours have been previously described (Grayzel and Friedman, 1941; Marwil and Beaver, 1942). An Aschheim-Zondek test was performed on the third woman. The oestrogen reaction in this case was so great that it raised the possibility of an early pregnancy although this was disproved by laparotomy and curettage, the endometrium showing secretory activity without evidence of pregnancy or recent abortion.

Although there are several features which suggest a possible hormonal influence these are limited to a small proportion of the cases. Nevertheless it is of importance to investigate all patients with solid ovarian tumours presenting with abnormal vaginal bleeding as it is by this means that any hormonal effects of Brenner tumours will be proved.

Summary

Thirty-one Brenner tumours from 30 patients have been investigated. The endometrium from 19 of these patients was examined. A little more than half the patients complained of abnormal vaginal bleeding. One patient had an endometrial adenocarcinoma and 6 patients had endometrial hyperplasia. A thecoma was present in 1 of these cases and a follicular cyst in another.

The possible endocrine influence of Brenner tumours is discussed and it is considered that several features suggest such an effect but further investigation of new cases is required before any firm conclusions can be drawn.

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UTERUS BICORNIS UNICOLLIS COMPLICATED BY PREGNANCY IN A RUDIMENTARY HORN AND WITH SUBSEQUENT NORMAL PREGNANCY

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PREGNANCY in a rudimentary horn was first described by Vassal and Mauriceau in 1669 (quoted by Mulsow, 1945). However, Sanger was the first to collect reported cases and his publication in 1883 emphasized that the natural course of such a pregnancy was rupture of the gravid horn at about the fourth month. Although this is the usual gestation period at which rupture occurs, Duff (1914) reported one case at the fifth week and several cases have been reported in which pregnancy reached full term (Colucci, 1952; Candello, 1958).

The condition is rare and Latto and Norman (1950) state that about 200 cases had been reported. They were able to find reference to 40 cases reported in the period 1925–50. In the *Index Medicus* for the past 10 years I have been able to find a further 22 cases. Of these 22 cases, only 2 were diagnosed pre-operatively, the remainder being considered to be tubal pregnancies, although the gestation period was in 18 cases at 16–20 weeks.

It is often stated that the rudimentary horn does not usually communicate with the uterine cavity. Pregnancy in the horn is then said to occur by external migration of the spermatozoa or of the fertilized ovum (Kerr and Moir, 1949). Keherer in 1900 collected 84 cases from the literature and stated that in 78 per cent the rudimentary horn did not communicate with the uterine cavity. The specimens were not, however, examined histologically. Latto and Norman (1950) point out that for fertilization to occur by migration of spermatozoa, several millions of them would have to cross the peritoneal cavity. They also state that transmigration of the ovum is unlikely as in most reported cases the corpus luteum has been on the same side as the rudimentary horn. However, transmigration must occur occasionally and accounts for cases such as that reported by Taber (1950) in which pregnancy occurred in a rudimentary Fallopian tube which was not connected at all to a uterus unicornis.

CASE REPORT

The patient was admitted to the Cardiff Royal Infirmary on 21st October, 1958, complaining of severe abdominal pain of 3-hours duration. She had experienced slight pain across the lower abdomen for the previous 3 days, but this had suddenly become more severe. One hour before admission she had felt faint and had vomited once. She was a primigravida, aged 22 years, married for 7 months. The last menstrual period occurred on 18th June, 1958, and, her normal cycle being regular, she was at the 17th week of pregnancy.

On examination the patient was obviously distressed with pain. The skin was cold, sweating and pale. The pulse rate was 140 per minute and the blood pressure 80/55. The abdomen was slightly distended and extremely tender to touch. It was possible to make out an indefinite mid-line swelling arising from the pelvis and reaching to the umbilicus. Bimanual examination was unsatisfactory because of the tenderness and rigidity. A provisional diagnosis of ruptured ectopic pregnancy was made and arrangements made for laparotomy and blood transfusion. A total of 4 pints of blood and 1 pint of plasma were transfused during and after the operation.

Under general anaesthesia the abdomen was opened. The peritoneal cavity contained 6 pints

of blood which was aspirated. Arising from the pelvis was a bicornuate uterus, the left horn being pregnant and ruptured. The gestation sac was still intact and there was free bleeding from the edge of the ruptured horn. The left horn was removed together with the left tube and gestation sac, leaving the left ovary. The uterine wound was closed by interrupted catgut sutures and the area covered with peritoneum. The patient's general condition had considerably improved by the end of the operation and the post-operative period was uneventful.

Histological examination of the base of the excised horn revealed: "A minute canal not visible macroscopically, lined by a simple tubal-type epithelium and surrounded by hyperplastic uterine muscle" (Fig. 1).

A hysterosalpingogram was performed on 7th January, 1959, and showed a normal-sized cavity in the remaining horn and a patent Fallopian tube (Fig. 2).

Subsequent Pregnancy

The patient was advised not to conceive within 6 months of the operation. She became pregnant in June, 1959 and the pregnancy was normal throughout. On 29th March, 1960, three days past term, after a labour lasting 13 hours, she delivered spontaneously a healthy infant weighing 6 pounds 14½ ounces. The uterine scar gave no cause for anxiety during labour.

Comment

Two points seem worth emphasis:

(1) The mechanism by which pregnancy occurs in a rudimentary horn, i.e., external migration of spermatozoa or of the fertilized ovum, probably occurs much less commonly than formerly thought. It is likely that histological examination of specimens showing no macroscopic connexion between the rudimentary horn and the uterine cavity, would demonstrate that such a connexion does exist, as in the case described.

(2) A pre-operative diagnosis should be made in most cases if it is remembered that the clinical picture is of a "classical" ruptured ectopic pregnancy preceded by 16–22 weeks amenorrhoea.

Summary

A case is described of rupture of the rudimentary horn of a bicornuate uterus at the seventeenth week of pregnancy, and of a subsequent normal pregnancy in the remaining horn. The literature on the subject is briefly reviewed, with particular reference to the mechanism of fertilization and the pre-operative diagnosis.

Acknowledgments

I am grateful to Professor A. S. Duncan and Mr. M. D. Arwyn Evans for permission to record this report.

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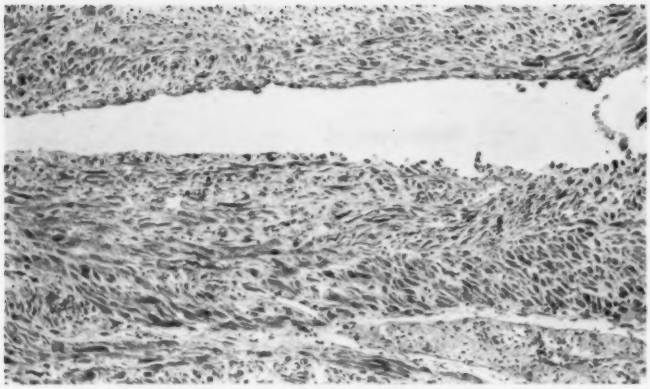

FIG. 1

Section through base of excised horn showing canal lined by simple epithelium. ×66.

FIG. 2

Hysterosalpingogram taken 3 months after operation.

AN ECTOPIC VAGINAL URETER

BY

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AN accessory ureter is a common urological anomaly in both sexes. Its orifice is frequently intravesical but on rare occasions in the female it is extravesical, in the posterior urethra (Brockis, 1952), in the vestibule (Dodd, 1950) or in the vagina (Hunter, 1932). Rarer still it may have an extravesical opening in the vagina and an intravesical opening at the apex of the trigone.

HISTORY

The patient was a married woman of 42 years. Her complaint was that she was always wet, and always had been as long as she could remember and had to wear towel protection even when in bed. She passed urine in normal amounts and regularly and there was no history of frequency of micturition or dysuria.

The previous medical history was of appendicectomy and herniorrhaphy when she was 20.

The menstrual cycle was regular 5/28.

There were no children and no miscarriages.

General Examination

She was a well nourished and well developed woman in good health. The cardiovascular, respiratory and central nervous systems were normal. The urine was normal.

Pelvic Examination

The vulva was normal. The vaginal orifice was relaxed. The vagina was healthy but was noticeably wet. There was a slight cystocele. The cervix was healthy and descended to the introitus. Bimanually the uterus and adnexa were normal. Stress incontinence of urine was not demonstrated. The history and the physical findings suggested a urinary fistula and the patient was admitted for investigation.

Investigations

(1) *Catheter specimen of urine.* This was normal and sterile on culture.

(2) *Vaginal examination.* A careful search of the vagina revealed a papilla on the anterior vaginal wall in the middle line near the cervix. On probing it a fluid like urine leaked from it.

(3) *X-ray examinations.* (*a*) Retrograde injection of contrast media through the ectopic opening showed a thick tortuous tube extending from the pelvis to the loin on the left side. This suggested an accessory ureter (Fig. 1). (*b*) Intravenous pyelogram following the retrograde injection showed that the right kidney pelvis was normal. The lower calyces of the left kidney were normal. The accessory ureter served only a hydronephrotic upper main calyx on the left side and this was entirely separate from the normal lower calyces (Fig. 2).

(4) *Intravenous indigocarmine.* Urine drawn from the bladder 20 minutes after the injection was tinged blue but there was no observable dye in the fluid which leaked from the accessory ureteric opening in the vagina.

(5) *Cystoscopy.* The bladder was normal. Both ureteric orifices were normal in position and were functioning. No abnormal opening was seen.

Diagnosis and Treatment

Investigation showed that the accessory ureter served only the upper main calyx of the left kidney. As the calyx was separate from the lower calyces, and was hydronephrotic and presumably non-functioning, a heminephrectomy was thought advisable.

Operation

Through an oblique incision in the loin the hydronephrotic part of the left kidney was removed along with the dilated ureter down to the level of the pelvic brim.

Progress

The patient made an uneventful recovery and seemed cured at the post-operative examination 3 months later when she was discharged.

Two years later she returned with a recurrence of symptoms which she had first noticed about a year previously so she was again admitted to hospital for further investigation.

General Examination

The patient was in good general health.

Pelvic Examination

The vulva and vagina were markedly wet. There was now a second degree of genital prolapse with a large cystocele, a small rectocele and the cervix protruded further from the introitus. The opening of the accessory ureter on the anterior vaginal wall was easily seen and urine gushed from it when the patient coughed (Fig. 3).

Investigations

(1) *Catheter specimen of urine.* A coliform infection was found and treated.

(2) *X-ray investigations.* (*a*) Retrograde injection of contrast media through the ectopic opening was repeated. This outlined the remaining part of the accessory ureter much better than before. There was a marked constriction about the level of the internal cervical os and, as the sac below this filled, contrast media was seen to enter the bladder.

A connexion between the accessory ureter and the bladder was thus established (Fig. 4).

(*b*) A uterogram done at the same time as the retrograde injection showed more clearly the contrast media in the bladder and an elongated cervix and a hypoplastic body of uterus of normal shape (Fig. 5).

(3) *Cystoscopy.* A cystoscope was passed into the bladder through the urethra and the accessory ureter was filled with indigocarmine from the opening in the vagina. The dye was seen to enter the bladder in the middle line at the apex of the trigone. The orifice was a very small one and several attempts to catheterize it failed. The mucosa around the opening was normal. The rest of the bladder was normal.

Diagnosis and Treatment

Investigations showed that the accessory ureter had an intravesical and an extravesical opening producing an unusual type of fistula between the bladder and the vagina. It was obvious that to effect a cure the remaining part of the accessory ureter should be removed and its connexion with the bladder closed.

Operation

The remaining accessory ureter was exposed extraperitoneally through an oblique incision about one inch above and parallel to the left inguinal ligament.

The accessory ureter was easily identified as its course was followed into the pelvis. It ran medial and posterior to the normal left ureter and superior to the uterine artery and entered dense fibrous tissue at the side of the cervix. This part was dissected free down to the cervix. The opening in the anterior vaginal wall was then identified and excised and the tract dissected upwards until its connexion with the bladder was demonstrated. It was then ligated, divided and oversewn. The opening in the vaginal vault was closed with interrupted sutures. The bladder was filled with water and, as none leaked into the operation site, the wound was closed in layers over a rubber drain. At the end of the operation fluid from the bladder was clear but a catheter was left in place for the purpose of continuous drainage.

Progress

The post-operative course was uneventful and there was no evidence of urinary incontinence. Six months later a Manchester repair operation was performed for cure of the genital prolapse, and this was uneventful.

When last seen 4 years after operation the uterus and vaginal walls were well supported,

FIG. 1

A retrograde ureterogram of the accessory ureter.

FIG. 2

A retrograde ureterogram of the accessory ureter combined with an intravenous pyelogram. The accessory ureter served only a hydronephrotic upper main calyx on the left side.

FIG. 3

The vaginal orifice of the accessory ureter is clearly seen.

FIG. 4

A retrograde ureterogram of the remaining accessory ureter showing a marked constriction about the level of the cervix, and as the sac below this was filled contrast media entered the bladder.

FIG. 5

A uterogram done at the same time as the retrograde ureterogram showed more clearly the contrast media in the bladder and an elongated cervix and hypoplastic body of uterus of normal shape.

there was no urinary incontinence, and she was symptom-free.

Discussion

Aetiology

In the absence of any history of surgical or obstetric trauma there can be little doubt that the condition was a "congenital" one.

Embryology

The Wolffian or mesonephric duct which becomes the epididymis, vas deferens and seminal vesicles in the male, is vestigial in the female. It gives off an outgrowth which becomes the ureter and the terminal lower part of the duct forms the trigone of the bladder in both sexes, and the prostatic urethra in the male, and the posterior wall of the urethra in the female (Hamilton, Boyd and Mossman, 1945; Brockis, 1952). The vestigial remnants which regularly persist are the hydatids of Morgagni, the epoöphoron and the paroöphoron. They are found in the broad ligament below the Fallopian tube. More rarely a further remnant, the duct of Gärtner, persists (Greig and Herzfeld, 1927). This lies in the mesosalpinx, reaches the cervix which it penetrates superficially and proceeds down the lateral vaginal wall to end in the vestibule. In the female, therefore, a ureter may end in the trigone, the urethra or the vestibule by remaining attached to the Wolffian duct. When an accessory ureter forms it too may end in any of these positions. On some occasions a ureter actually drains into the vagina. There is no embryological explanation for this unless one postulates a break-through between the Müllerian and Wolffian systems, and this would account for it simply if it is accepted that at an early stage of development both systems lie in a common sheath (Gruenwald, 1941). If the orifice of a persistent Wolffian duct is late in forming or becomes stenosed, the distended duct may perforate the wall of the Müllerian duct and drain into what will become the cervix or the vagina. An accessory ureter which remains attached to a persistent Wolffian duct may therefore have two openings, one along the course of the Wolffian duct, and the other into the vagina or cervix. This is the explanation offered to account for the accessory ureter in the case described, which had an intravesical opening at the apex of the trigone and an extravesical opening into the vagina.

Diagnosis

Innes Williams (1954), in discussing the diagnostic problem set by the ectopic ureter, points out the limited value of intravenous pyelogram and the intravenous indigocarmine test, because so often the ectopic ureter is serving a non-functioning or poorly functioning part of the kidney. He also draws attention to the difficulty of finding an ectopic opening in the vagina and of doing a retrograde ureterogram in the child and adolescent girl. There was no such problem in this case.

Many authors mention the tortuous nature of an accessory ureter, the tract often being a series of dilatations. This makes it difficult to pass a retrograde catheter for any great distance. This case illustrates how important it is that the accessory ureter should be filled in its entirety if a possible second and intravesical opening is always to be excluded.

It is usually possible to see the intravesical opening of an accessory ureter at cystoscopy but again this is not always so because of the position of the opening at the apex of the trigone or because it is small and stenosed.

In the case described the intravesical opening was small and probably valvular, hence the temporary cure of incontinence after the first operation. Progressive descent of the prolapse presumably destroyed the valvular action and resulted in a return of urinary incontinence. The dye in the bladder test was not done in this case, but if it had been it might have given a false negative result for fistula until the prolapse destroyed the valvular nature of the intravesical opening.

Summary

A case of an accessory ureter with an intravesical and an extravesical opening is described. As there was no history of surgical or obstetric trauma the condition was presumed a "congenital" one.

An embryological explanation is offered and

the diagnostic problem set by such cases is discussed.

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DIZYGOTIC ANENCEPHALIC TWINS (MICROCEPHALY CRANIORHACHISCHISIS)

Case Report

BY

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THE study of malformations occurring in twin pregnancies has been used to throw some light on the factors concerned in the aetiology of such malformations, and in particular to determine which of the two major factors, heredity or environment, has the greater influence. Malformations of purely genetic origin should affect identical twins similarly, but environmental factors might be expected to produce dissimilarity at times. Although anencephaly has frequently been recorded affecting both of monozygotic twins, and less frequently affecting only one of monozygotic twins, this particular malformation affecting both of dizygotic twins does not appear to have been previously recorded. The following case is reported because it is believed to be the first of its kind; furthermore, concordant malformations in dizygotic twins have only infrequently been recorded.

CASE REPORT

Mrs. J.S., aged 20 years, para-2, was first seen at the antenatal booking clinic on 6th October, 1958, when she gave a history of 12-weeks amenorrhoea. Her first baby, born in 1956, was delivered by forceps, and weighed 6 pounds 9 ounces; her second baby, born in 1957, was delivered spontaneously at 39 weeks gestation, and weighed 4 pounds 4 ounces. Both pregnancies were complicated by pre-eclampsia. Her previous health had been good, apart from appendicectomy at the age of 13 years. Her mother was a diabetic, and there was a history of twins both in her own family, and that of her husband.

Her pregnancy had so far been uneventful, apart from some morning sickness, and there was no history of infection or contact with infectious diseases. General examination revealed no significant abnormality; her height was 5 feet 4 inches, weight 126 pounds, and blood pressure 130/78.

Abdominal and vaginal examination revealed that the uterus was enlarged to a size corresponding to a fourteen-week gestation, i.e., larger than her dates suggested. The blood group was A Rhesus positive, Wassermann reaction negative, haemoglobin 78 per cent, urine free of albumin and sugar, and a chest X-ray was negative.

The patient was booked for confinement, and requested to attend the antenatal clinic in six weeks time. However, she failed to do so, and her whereabouts could not be traced.

On 11th February, 1959, she was admitted to the Maternity Unit when she was well advanced in labour; the gestation period was 30 weeks 4 days. Labour had started at 9 a.m. that morning, and her membranes had ruptured spontaneously at 9.45 a.m. when a large quantity of liquor had drained. On admission at 11 a.m. her blood pressure was 130/90, and there was slight oedema of the legs. The fundus uteri was three-fingers below the xiphisternum, the uterus was tense and it was difficult to distinguish foetal parts or to hear the foetal heart sounds.

At 11.20 a.m. the cervix was fully dilated and the first twin, together with its attached placenta, was delivered spontaneously at 11.35 a.m. by very strong maternal effort, assisted by traction on the anterior shoulder of the foetus. The presentation was a face, mento-anterior, and the foetus was a stillborn anencephalic female infant weighing 816 grammes. A very large exomphalos was present, to which the placenta was attached by a short cord running over the surface of the sac.

Following the delivery of the first twin, the membranes of the second sac were ruptured artificially, releasing a large quantity of liquor amnii (about 40 to 50 ounces). The second twin was delivered spontaneously at 11.50 a.m. the presentation being a face, mento-anterior; the second twin was also an anencephalic female infant and weighed 1,030 grammes. The placenta and membranes

of the second twin were delivered separately at 11.55 a.m. with a total blood loss of 5 ounces. The second twin made no attempt to breathe, but a cardiac impulse was present for 50 minutes.

The puerperium was complicated by a moderate degree of iron-deficiency anaemia but, apart from this, was uneventful, and the patient was discharged on her 9th day.

Post-mortem Examination

The First Twin

The head showed the features of anencephaly, with a small quantity of brain tissue lying on the skull, covered by haemorrhagic membrane; the appearance corresponded to the variation of anencephaly known as microcephaly craniorhachischisis (Macgregor, 1960). The pituitary gland was present lying in a shallow fossa on the base of the skull. The spine was bifid in the upper thoracic and cervical regions.

There were some interstitial haemorrhages of the lung, otherwise the thoracic organs were unremarkable. A large exomphalos was present with a defect in the abdominal wall and the intestine lying exposed. Both adrenals were typically minute; the other abdominal organs showed no abnormality.

The Second Twin

The head showed a variation from the first twin, in that the frontal bones were more developed and partly covered the base of the skull, but the appearance was similar to the first twin, and corresponded to that of microcephaly craniorhachischisis. There was no brain tissue underlying the frontal bones, but a pituitary fossa was present containing an apparently normal pituitary gland. The occipital bones were entirely absent, and protruding from the back of the skull was a mass of haemorrhagic brain tissue. The spine was bifid in the cervical and thoracic regions.

The thoracic organs were unremarkable apart from interstitial haemorrhages into the lungs. The adrenals were both of the usual minute anencephalic type, otherwise the abdominal organs were normal.

The Placenta and Membranes

The placenta of the first twin was delivered in continuity with the foetus and was attached by a short cord measuring 4 inches long, which was stretched over the surface of a large exomphalos.

The placenta of the second twin was delivered separately after the birth of the second foetus. It weighed 245 grammes, and the cord, which was inserted eccentrically, measured 16 inches long. The placenta was unremarkable.

Review of the Literature

Malformations in separate twins may be divided into the following groups:

(1) Monozygotic twins:

(*a*) Concordant or similar malformations.

(*b*) Discordant malformations usually affecting only one twin; the other twin is almost always normal.

(2) Dizygotic twins:

(*a*) Concordant.

(*b*) Discordant.

(3) Special types of malformation occurring in twins such as:

(*a*) Foetus compressus or papyraceus.

(*b*) Acardiac foetus.

The case described here is an example of concordant malformation occurring in dizygotic twins, and no other case, in which both of dissimilar twins were anencephalic, has been found on record in the literature. There are, however, many other types of concordant malformations occurring in dizygotic twins.

Mongolism in both of dizygotic twins is recorded five times, namely by Russell (1933), MacKaye (1936), Gordon and Roberts (1938), Jervis (1943) and Nicholson and Keay (1957). Paraplegia was associated with mongolism in the twins described by Gordon and Roberts, and the twins of Nicholson and Keay provide one of the rare examples of concordant malformation occurring in twins of opposite sex. Pyloric stenosis in dizygotic twins has been recorded by O'Donnell and Klein (1941) and Laubschen and Smith (1947); Hughes *et al.* (1949) described the condition occurring in twins of opposite sex.

Hydrocephaly and spina bifida in dizygotic twins is reported by Stroink (1937) and by Fry (1943). Birkenfeld (1927) recorded harelip and

FIG. 1
Dizygotic anencephalic twins (microcephaly craniorhachischisis).

cleft palate occurring in dissimilar twins of opposite sex, and Shea and Nelson (1947) described twins, one with bilateral harelip, and the other with a unilateral harelip and cleft palate. Torgersen (1948) recorded dizygotic twins, one with complete situs inversus, and the other with partial situs inversus affecting the stomach only. Bertoye *et al.* (1952) described dissimilar twins with congenital heart disease.

Many of the cases recorded in the literature have not been mentioned because of the lack of information about the placenta and membranes and the type of twinning. The criteria for classifying twins as monozygotic or dizygotic are rather slender even in some of the cases quoted here. Only 3 cases are recorded in which the twins were of opposite sex. The criteria which have been accepted by other authors include the appearance of the placenta and membranes, or the dissimilarity of phenotype, including finger-prints in some cases. However, it is well known that the dissimilarity of phenotype does not always give acceptable proof that the twins have arisen from separate ova, and the appearance of the placenta and membranes may be misleading, for about 5 per cent of all dichorionic, diamniotic twins are monozygotic, according to Willis (1958).

Discussion

Concordant malformations occur far more frequently in monozygotic twins than in dizygotic twins, and some authors believe that this affords conclusive proof that an anomaly is genetic in origin rather than environmental. The finding of discordant malformations in identical twins suggests, however, that environmental factors may play a more important part than had been formerly supposed, and Potter (1952) records two cases in which malformations affected only one of identical twins, one a case of anencephaly with a normal twin, and the other a case of multiple skeletal and visceral anomalies with a normal twin. She makes the following statement ". . . the presence of one malformation and one normal foetus would seem to invalidate this belief (that malformations are genetically transmitted) and the cause of malformation in these instances, at least, would seem of necessity to be some factor other than the genetic constitution."

In the case of dizygotic twins, the conclusion drawn from the presence of concordancy or discordancy may be just as variable. Fry (1943), in describing his case of twins with spina bifida, comes to the conclusion that "the cause of spina bifida is primarily a defect in the development of mesoblastic tissues from which the spinal meninges are produced, and this is the only factor that is likely to affect equally the two separate ova, rather than the mechanical agents or the external influences mentioned in several theories advanced". However, the fallacy of this argument has now become obvious, for the cause might not so readily have been ascribed to genetic factors, if the mother had been subjected to pelvic irradiation or had suffered from an attack of rubella during her pregnancy. Other environmental factors are still being discovered, and Bertoye *et al.* (1952) believe that an attack of maternal mumps during the second to third month of pregnancy could have been responsible for the congenital cardiac defects they described in dizygotic twins.

Although twin studies may be of value, Willis (1958) has pointed out some of the fallacies, for identical twins share a closely similar environment, more so than unlike twins, and each will therefore be more likely to respond to the same environmental factors. The subject is a very complex one, and many factors may contribute to the confusion regarding aetiology. The expressivity and penetrance of genes accounts for much of the confusion associated with the hereditary pattern of certain anomalies, and also the fact that a harmful gene may be present in normal persons but is handed down through one generation to another before it becomes linked with a similar gene and the anomaly is manifested. On the other hand, environmental factors have only emerged as the cause of malformations in recent years, and it seems likely that many such factors will be discovered in the future. It is possible that the answer lies somewhere between these two views, and that some alteration of environment, perhaps even a minor degree of anoxia, may set the stage for a harmful gene, normally of low penetrance, to express itself and exert its undesirable effect.

Animal experiments carried out by Anderson (1949) have, in fact, already demonstrated this phenomenon, and he was able to increase the incidence of malformation in the offspring of a breed of rats with a genetjc predisposition to diaphragmatic hernia by feeding them on a diet deficient in vitamin A during pregnancy.

Summary

(1) A case of dizygotic anencephalic twins is described. The twins were of the same sex, but were classified as dizygotic because the placentas were completely separate, the placenta of the first being delivered before the birth of the second twin.

(2) The literature relating to concordant malformation in dizygotic twins is reviewed. As far as can be ascertained, this is the first case of anencephaly affecting both of dizygotic twins, to be recorded.

(3) The fallacy of attributing malformations solely to genetic causes has been discussed.

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Addendum

Since this paper was submitted for publication another case of dizygotic anencephalic twin pregnancy has been reported by Lewis (1960).

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COMPOUND PRESENTATION

A Review of 91 Cases

BY

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COMPOUND or complex presentation is not very rare in obstetric practice, yet it is not common enough to give an individual obstetrician considerable experience on the condition. The literature on the subject is surprisingly scarce. Although a number of case records have been published, on searching the available literature, we have found only one paper dealing with a series of cases (Goplerud and Eastman, 1953). The following analysis of 91 cases of vertex presentation with prolapse of limbs, which occurred in Chittaranjan Sevasadan College Hospital during the years 1951 to 1959, indicates some of the difficulties which may arise and the results that were obtained.

TYPES

Prolapse of the upper limb was the commonest type in this series. It constituted 65·9 per cent of the total cases as compared with 90·2 per cent of cases of the series of Goplerud and Eastman. The next common variety was combined prolapse of upper and lower limbs that occurred in 22 per cent of the cases. In 12·1 per cent of the cases, the lower extremity was prolapsed. Prolapse of the cord was associated in 27·5 per cent of the total cases (Table I).

INCIDENCE

Ninety-one cases of vertex presentation with prolapse of limbs were reviewed during a period when there were 66,821 deliveries in the hospital, giving an incidence of 1 in 734 (Table II). This incidence, while lower than that given by McCormick (1947) (1 in 250–300), resembles

TABLE I

Types

Types	Goplerud and Eastman		Present Series	
	No. of Cases	%	No. of Cases	%
Hand	55	90·2	59	64·8
Both hands	Nil	Nil	1	1·1
Foot	2	3·3	11	12·1
Hand and foot	4	6·5	18	19·8
Hand and both feet	Nil	Nil	1	1·1
Foot and both hands	Nil	Nil	1	1·1
Associated cord prolapse	15	23·07*	25	27·5

* Including 4 cases of breech.

TABLE II
Incidence

Authors	Total	Hand	Foot	Hand and Foot
Gibberd (1955)	1:800			
McCormick (1947)	1:250–300			
Greenhill (1955)	1:350			
Goplerud and Eastman (1953)	1:695	1:744	1:21205	1:10602
Present series	1:734	1:1114	1:6075	1:3341

that of Gibberd (1955) and Goplerud and Eastman (1953).

The incidence of the different types in this series with the comparable figures of Goplerud and Eastman (1953) are given in Table II, from which it can be seen that the incidence of hand prolapse in these cases is less, whereas that of foot prolapse alone or combined type is about 3 times higher in this series.

PREDISPOSING FACTORS

Parity. Primigravidae constituted 12 per cent of the total cases and multigravidae 88 per cent, the corresponding figure in Goplerud and Eastman's series being 25 per cent and 75 per cent respectively (Table III). During the period of review, 19,091 primigravidae and 47,730 multigravidae were confined and vertex presentation with prolapse of the limbs occurred 11 and 80 times respectively. Thus, the incidence was 1 in 1,736 in primigravidae and 1 in 597 in multigravidae.

TABLE III
Predisposing Factors

Predisposing Factors	No. of Cases	%
Parity:		
Primigravidae	11	12·0
Multigravidae	80	88·0
Non-engagement of head	77	85·0
Prematurity:		
Weight 5½ pounds or less	53	58·2
Weight less than 5 pounds	30	33·0
Multiple pregnancy:		
Twins	9	9·9
Triplets	2	2·2
Ante-partum haemorrhage:		
Placenta praevia	6	6·6
Accidental haemorrhage	1	1·1
Gross hydramnios	4	4·4
Contracted pelvis	3	3·3
Macerated baby	2	2·2

Non-engagement of Head. In 77 cases (85 per cent), the head was found unengaged at the time of diagnosis and in 46 cases (50 per cent) it was floating freely.

Prematurity. Fifty-three babies weighed not more than 5 pounds 8 ounces at birth, giving a prematurity rate of 58·2 per cent. In 33 per cent of cases the birth weight was less than 5 pounds.

Multiple Pregnancy. There were 9 cases of twins and 2 cases of triplets. With the exception of 1 case of twins, prolapse of a limb always occurred in the last-born baby.

Ante-partum Haemorrhage. Out of 7 cases of ante-partum haemorrhage 6 were due to placenta praevia of Types I and II. The remaining case was diagnosed as accidental haemorrhage.

Hydramnios. Three cases of single pregnancy and 1 case of twin pregnancy were complicated by gross hydramnios. Minor degrees of hydramnios were not taken into account because the quantity of liquor amnii was not recorded.

Contracted Pelvis. Contrary to expectation, contracted pelvis was found only in 1 primigravida and 2 multiparae with a bad obstetric history.

Macerated Baby. The foetal heart sounds were inaudible on admission in 28 cases in 2 of which the child was macerated.

Diagnosis

In all cases, the diagnosis was made only after the onset of labour. Of 20 cases admitted with intact membranes, compound presentation was diagnosed in 9 cases. In the remaining 11 cases, the limbs were detected after the membranes ruptured.

Complication

Pre-eclamptic toxaemia was associated in 8 cases and anaemia (below 40 per cent, Sahli) in 4 cases (Table IV).

Table IV
Complications

Complications	No. of Cases	%
Pre-eclamptic toxaemia	8	8·8
Anaemia	4	4·4
Jaundice	1	1·1
Cord prolapse	25	27·5
Prolonged labour (more than 48 hours)	11	12·1
Obstructed labour	10	10·9
Shock and severe dehydration ..	4	4·4
Post-partum haemorrhage	4	4·4
Retained placenta	1	1·1
Puerperal pyrexia	14	15·4
Retention of urine	12	13·2

One primigravida and 9 multigravidae were admitted with features of obstructed labour (10·9 per cent). Shock and dehydration of severe degree were present in 4 of these cases. The labour was prolonged for more than 48 hours in 11 cases (12·1 per cent) and for more than 24 hours in 17 cases (18·6 per cent). The third stage of labour was complicated by post-partum haemorrhage in 4 cases, in 2 of which manual removal of the placenta was done. In another case of retained placenta without haemorrhage the placenta was removed manually. Puerperal pyrexia occurred in 14 cases (15·4 per cent). There was retention of urine in 12 cases (13·2 per cent).

Maternal Mortality

There was one maternal death in a multigravida, who was admitted with obstructed labour and in a low condition. She was a case of vertex presentation with prolapse of the upper limb. After resuscitation, a craniotomy was done. She developed severe post-operative shock and expired after 21 hours. No post-mortem was done.

Foetal Wastage

The perinatal death rate was 46·2 per cent and stillbirth accounted for more than 80 per cent of these deaths (Table V). The corresponding figure in cases complicated by cord prolapse was 60 per cent as compared with 40 per cent in those cases where only limbs prolapsed.

There were 28 cases where the foetal heart sounds were inaudible at the time of admission; if these cases are excluded, the perinatal mortality rate would be 22·2 per cent. When a correction is made for 7 premature babies weighing less than 4 pounds and 3 cases of cord prolapse, the perinatal death, stillbirth and early

Table V
Foetal Wastage

	Total No.	Perinatal Death	Stillbirth	Early Neonatal Death
All cases	91	42 (46·2%)	35 (38·5%)	7 (7·7%)
Cases admitted with living foetus	63	14 (22·2%)	7 (11·1%)	7 (11·1%)
Corrected	53	4 (7·54%)	1 (1·9%)	3 (5·66%)

TABLE VI

Causes of Death	Stillbirths	Early Neonatal Deaths
Prematurity	3*	4†
Infection	–	1
Birth trauma	–	1‡
Cord prolapse	1	–
Cord prolapse with moderate pre-eclamptic toxaemia	2	–
Unexplained foetal distress	1	1

* Birth weights: 2 pounds 2 ounces; 1 pound 3 ounces; 3 pounds 14 ounces.
† Birth weights: 2 pounds; 2 pounds 3 ounces; 2 pounds 8 ounces; 3 pounds.
‡ Due to a difficult mid-forceps delivery.

TABLE VII
Rate of Interference

	All Cases	Cord Prolapse	Hand	Foot	Hand and Foot
Non-interference	24 (26·3%)	0 (0·0%)	19 (35·1%)	1 (12·5%)	4 (25·0%)
Interference	67 (73·7%)	13 (100·0%)	35 (64·9%)	7 (87·5%)	12 (75·0%)

neonatal death rates become 7·54, 1·9 and 5·66 per cent respectively. Table VI shows the cause of perinatal death in 14 cases.

MANAGEMENT

Initial resuscitative measures to combat shock and dehydration were necessary in 4 cases of obstructed labour.

Spontaneous vaginal delivery as compound presentation occurred in 1 out of 11 primigravidae (9·1 per cent) and 23 out of 80 multigravidae (28·7 per cent), without any interference except episiotomy. Thus, no interference was done in 26·3 per cent of the total number of cases (Table VII).

While the rate of interference was 73·7 per cent in all cases, it was 100 per cent in cases complicated by cord prolapse with a living foetus. In the remaining cases that included cord prolapse with a dead foetus, the rate of interference was 64·9 per cent, 87·5 per cent and 75 per cent in hand prolapse, foot prolapse and combined hand and foot prolapse cases respectively.

In these cases interference was done either in the form of a corrective manœuvre, such as reposition or internal podalic version by which a more favourable presentation was obtained or in the form of operative delivery such as Caesarean section or craniotomy without any preliminary corrective measures. In some cases both corrective manœuvre and operative delivery were undertaken.

Amongst 67 cases of interference, natural unaided vaginal delivery occurred in 33 cases—24 cases after reposition of limbs, 8 cases after internal podalic version and one case after bipolar podalic version (Table VIII). In 4 cases forceps delivery was performed immediately after reposition. The breech was extracted in 18 cases following internal podalic version. Lower segment Caesarean section was done in one multipara for contracted pelvis. In 8 cases of obstructed labour craniotomy was done. Reposition followed vaginal delivery aided with continuous scalp traction by Willett's forceps in 3 cases, 2 of which were placenta praevia.

Thus, reposition of the limb was done 31 times (34 per cent), internal podalic version 26 times (28·7 per cent) and destructive operation 8 times (8·7 per cent) in this series.

TABLE VIII
Method of Treatment

Method of Treatment	All Cases	Parity		Limb Prolapse				Limb Prolapse with Cord Prolapse			
		Primi	Multi	Total	Hand	Foot	Hand and Foot	Total	Hand	Foot	Hand and Foot
Non-interference	24	1	23	24	19	1	4	Nil	Nil	Nil	Nil
Reposition and spontaneous delivery	31 24	3	21	21	16	Nil	5	3	Nil	2	1
Forceps delivery	4	2	2	3	3	Nil	Nil	1	1	Nil	Nil
Willett's traction	3	1	2	2	1	Nil	1	1	1	Nil	Nil
Internal podalic version and spontaneous delivery	26 8	0	8	8	5	1	2	1	Nil	1	Nil
breech extraction	18	2	16	10	3	4	3	7	4	Nil	3
Bipolar podalic version and natural delivery	1	Nil	1	1	Nil	Nil	1	Nil	Nil	Nil	Nil
Craniotomy	8	2	6	8	7	1	Nil	Nil	Nil	Nil	Nil
Lower segment Caesarean section	1	0	1	1	Nil	1	Nil	Nil	Nil	Nil	Nil
Total No.	91	11	80	78	54	8	16	13	6	3	4

Compound Presentation with Prolapse of the Cord. There were 25 cases, where, together with the limbs, the cord was also prolapsed. In 12 cases the foetus was dead at the time of admission. They were treated as if there were no cord prolapse. Interference was carried out in all the 13 cases where the foetal heart sounds were audible on admission (Table VII). In 5 of these cases reposition of limb and cord was possible and was followed by natural delivery in 1 case of hand and foot prolapse and two cases of foot prolapse, by forceps delivery in a case of hand prolapse and by Willett's scalp traction forceps in a similar case. The breech was extracted after internal podalic version in 4 cases of hand prolapse and 3 cases of hand and foot prolapse and there were 1 and 2 stillbirths respectively. In the remaining case of foot prolapse, internal podalic version was done and a living baby was delivered spontaneously as breech (Table VIII).

Compound Presentation Uncomplicated by Prolapse of the Cord. This group consisted of 78 cases and included 12 cases of cord prolapse where the foetus was dead at the time of admission.

Hand Prolapse. In 19 out of 54 cases, spontaneous vaginal delivery was allowed (35·1 per cent). Reposition of the limb was done in 20 cases; of these natural delivery occurred in 16 cases, forceps delivery in 3 cases and delivery by continuous scalp traction in one case of placenta praevia. Internal podalic version was followed by natural delivery in 5 cases and breech extraction in 3 cases. Craniotomy was performed in 7 cases.

Foot Prolapse. Spontaneous vaginal delivery without any interference occurred in only 1 out of 8 cases. Internal podalic version was done in 5 cases and was followed by natural delivery in 1 case and breech extraction in 4 cases. One case each was treated by lower segment Caesarean section and craniotomy.

Combined Prolapse of Hand and Foot. In 4 out of 16 cases spontaneous vaginal delivery was allowed. In 5 cases natural delivery followed reposition. Willett's forceps was used after reposition in one case of placenta praevia. Out of 5 cases of internal podalic version, the breech was extracted in 3 cases and natural delivery occurred in 2 cases. One case had a natural delivery following bipolar podalic version.

Discussion

Analysis of this series shows that there was a high incidence of obstructed labour (11·1 per cent), prolonged labour (12·1 per cent) and foetal wastage (46·2 per cent). There was one maternal death in a case complicated by obstructed labour. In view of these grave risks, it appears that in common textbooks less consideration has been given to this condition than it deserves.

Diagnosis during pregnancy is unusual and is possible only by skiagraphy. In such cases, it is important to exclude contracted pelvis and placenta praevia. Admission into a hospital before the labour starts is advisable. Corrective procedure by abdominal manipulation (Percival, 1959) has been described but seems to be of doubtful value.

Most of the cases are diagnosed during labour. If the membranes are still unruptured, cord presentation is difficult to exclude. The foot end of the bed should be kept raised in these cases and a strict watch is to be kept on the foetal heart rate. A pelvic examination is essential as soon as the membranes rupture.

No interference is advisable in the first stage of labour, in absence of complication, such as contracted pelvis, cord prolapse and foetal distress. All authors agree that a watchful expectancy is to be continued in the second stage of labour in uncomplicated cases of hand prolapse in expectation of either spontaneous rectification or natural delivery as compound presentation, aided, if necessary, by low forceps only. In Goplerud and Eastman's series of cases, out of 21 cases thus treated, only one infant was lost. In the present series, spontaneous vaginal delivery as compound presentation occurred in 35 per cent of the cases of hand prolapse and there was no foetal loss in 13 uncomplicated cases of this group that were admitted with audible foetal heart sounds (Table IX). In prolapse of the foot, a similar line of treatment has been advocated in the hope of spontaneous vaginal delivery (McCormick, 1947). But from this analysis it appears that the chance of unaided delivery is remote. Out of the total 11 cases, unaided delivery occurred in one case only and that too was admitted with a dead foetus. In the combined type of prolapse, although McCormick does not expect spontaneous delivery, 4 out of the total 20 cases had unaided deliveries with one neonatal death in a baby weighing 2 pounds 3 ounces. The remaining 3 babies were mature and living.

In view of the satisfactory foetal result in unaided deliveries, it appears that, in uncomplicated cases of all types, watchful expectancy is indicated beyond the first stage of labour, unless

Table IX

Foetal Wastage in Relation to the Method of Treatment in Cases Admitted with Audible Foetal Heart Sounds

Method of Treatment	All Cases	Peri-natal Death	Hand		Foot		Hand and Foot	
			No. of Cases	Peri-natal Death	No. of Cases	Peri-natal Death	No. of Cases	Peri-natal Death
Spontaneous delivery	17	1	13	Nil	Nil	Nil	4	1*
Reposition and natural delivery	22	4	15	2*	2	Nil	5	2
Forceps delivery	4	1	4	1	Nil	Nil	Nil	Nil
Willett's traction	2	1	2	1*	Nil	Nil	Nil	Nil
Internal podalic version and natural delivery ..	5	1	2	Nil	2	1*	1	Nil
Breech extraction	11	5	7	3(1*)	1	Nil	3	2
Craniotomy	1	1	1	1	Nil	Nil	Nil	Nil
Caesarean section	1	Nil	1	Nil	Nil	Nil	Nil	Nil

* Birth weight=3 pounds or less.

the limbs prevent engagement of the head and delay or arrest the progress of the labour. Interference will, however, be necessary in most cases of foot prolapse and many cases of combined prolapse of hand and foot.

Reposition. Because of the low risk associated with this obstetric manœuvre, reposition of a limb is the method of choice when the above-mentioned indications are present provided the head and the limb are not engaged. In the latter case, forceps delivery without reposition is indicated. In Goplerud and Eastman's series, no infant was lost in 7 cases of hand prolapse treated by reposition. In the present series, out of 28 cases including 2 cases of foot prolapse and 5 cases of combined prolapse of hand and foot, 6 infants were lost, but 3 of these weighed 3 pounds or less. One of the remaining babies died after a difficult mid-forceps delivery in a primigravida. Two other neonatal deaths in multigravidae occurred in combined prolapse of hand and foot during natural delivery. In one of these cases the labour was prolonged for more than 48 hours. These deaths were not due to reposition and could possibly have been avoided by timely interference. After reposition, whether these cases should be left to nature for spontaneous delivery to occur or forceps should be applied, depends on whether immediate delivery is otherwise indicated. Routine forceps extraction to avoid recurrence of prolapse was not done in this series. Sixteen cases of hand prolapse, 2 cases of foot prolapse and 6 cases of combined prolapse of hand and foot had spontaneous vaginal delivery after successful reposition. In none of these cases did the prolapse of the limb recur (Table VIII).

Internal Podalic Version. This useful obstetric manœuvre has fallen into disrepute in recent years because of its associated risk of rupture of the uterus and high foetal wastage. While the danger of uterine rupture is real, it can be brought down to a minimum if performed in properly selected cases and with a reasonable gentleness. There was no such rupture in the 26 cases of internal podalic versions although these were performed mostly by the resident staff. Sixteen out of these 26 cases were admitted with living foetuses, 8 of which were uncomplicated by cord prolapse. Breech extraction was done in 3 of these cases with the loss of 2 babies and in the remaining 5 cases (2 hand, 2 foot and 1 combined prolapse where natural delivery was allowed) only one baby weighing 2 pounds 2 ounces died *in utero* in a case of placenta praevia. From this it seems that foetal wastage ascribed to internal podalic version is possibly not so much due to version itself as due to the breech extraction that follows. In uncomplicated cases internal podalic version alone as a method of changing the compound presentation to a more favourable one of breech is a safe procedure and is indicated where reposition fails. But where immediate delivery is necessary, Caesarean section should be given due consideration as an alternative treatment of version and breech extraction.

Caesarean Section. There is no indication of Caesarean section for compound presentation as such, unless a case is complicated by contracted pelvis, cord prolapse, foetal distress, etc. It is, however, a safer procedure in certain cases of obstructed labour with a thinned out lower segment even when the foetus is dead. As an alternative treatment to internal version followed by breech extraction, it should get a preference especially in primigravidae.

Craniotomy. This is indicated in cases of obstruction where the foetus is dead, provided the vaginal delivery is not likely to be difficult. In cases of doubt abdominal delivery is often preferable. The only maternal death of this series followed a craniotomy and could possibly have been avoided by a Caesarean section.

Summary

(1) Ninety-one cases of vertex presentation with prolapse of limbs were analyzed.

(2) This abnormal presentation was 3 times more common in multigravidae. Floating head, small baby and excess of liquor amnii were the main predisposing factors. Contracted pelvis was not a common association.

(3) Eleven per cent of cases were admitted with obstructed labour and 30·7 per cent with a dead foetus. Labour was prolonged beyond 48 hours in 12·1 per cent of cases.

(4) Spontaneous delivery as a compound presentation occurred in 26·3 per cent of the cases. In 73·7 per cent of the cases some form of interference was necessary.

(5) Spontaneous vaginal delivery was allowed in 33 out of 67 cases in which some form of interference was carried out. In the remaining cases operative delivery was done.

(6) The corrected perinatal mortality, stillbirth rate and neonatal death rate were 7·6, 1·9 and 5·7 per cent respectively. There was one maternal death due to obstructed labour.

Acknowledgments

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A GIANT DERMOID CYST

BY

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THE following case is recorded because of the unusual presenting symptom, the exceptional size of the cyst and the unusual gross appearances on section of the tumour.

Miss E.L., aged 58, a nullipara, was admitted to Worcester Royal Infirmary on 15th January, 1960, under the care of Mr. G. H. Marshall. Her complaint was of swelling of the left leg 2 weeks previously and less severe swelling of the right leg during the previous week. The abdomen was distended and it was thought that there was a central abdominal tumour. Vaginal examination was not very helpful, the cervix being high and out of reach. There was slight senile vaginitis, the menopause having occurred 12 years previously. In view of the possibility of a gynaecological lesion one of us (J.A.C.) was invited to examine the patient under anaesthesia along with Mr. Marshall and it was then possible to localize a cystic swelling filling the abdomen right down to the pelvis. She was transferred to the gynaecological ward at Ronkswood Hospital on 21st January, 1960. Laparotomy was undertaken on 22nd January, 1960. This showed that the swelling was a very large ovarian cyst, smooth and of benign appearance. It was semi-solid and after its removal was found to weigh 15½ pounds (7,000 g.). The uterus was small and atrophic with a number of small fibroids and the left appendage appeared normal apart from adhesions to the sigmoid colon, probably the result of pressure of the tumour mass. These adhesions were freed and a complete pelvic clearance carried out. During the post-operative period there was a mild deep vein thrombosis of the left calf which resolved rapidly with antispasmodic therapy and the patient left hospital in good condition on 8th February, 1960. When she was seen again on 9th March, 1960, the swelling of her legs had gone. She was pleased to report that she could eat bigger meals and walk better. There has been no further trouble.

The tumour measured $40 \times 33 \times 20$ cm.; it presented a smooth external surface except for a few old fibrous adhesions. The pedicle was short with the Fallopian tube of normal appearance. When the cyst was opened the internal lining was quite smooth and rather shiny though covered by a thin film of sebaceous material in which numbers of hairs were held. The bulk of the contents, however, was composed of irregular, rounded masses of pale brown, slightly greasy material, rather friable but of uniform colour and consistency. Again hair was incorporated in many of these masses. There was no free fluid or mucus.

The cyst wall was rather thin (0·2–0·3 cm.) except near the hilum where a separate locule containing yellow fat was found.

Sections taken from various parts showed a very simple dermoid pattern. Apart from the fatty tissue at the hilum only squamous epithelium with scanty associated sebaceous cysts was found lining the acellular collagenous cyst wall.

DISCUSSION

The presenting symptom of oedema of the leg is unlikely to have been caused by the main

mass which was related to the opposite side of the pelvis and was most probably due to pressure of the adherent left appendage and uterus displaced by the right-sided tumour. Although large dermoid cysts are occasionally seen the size of this tumour was exceptional and this may have been responsible for the curious "sack of potatoes" appearance shown in the figure (Fig. 1) and resulting from a coalescence of the sebaceous content of the cyst.

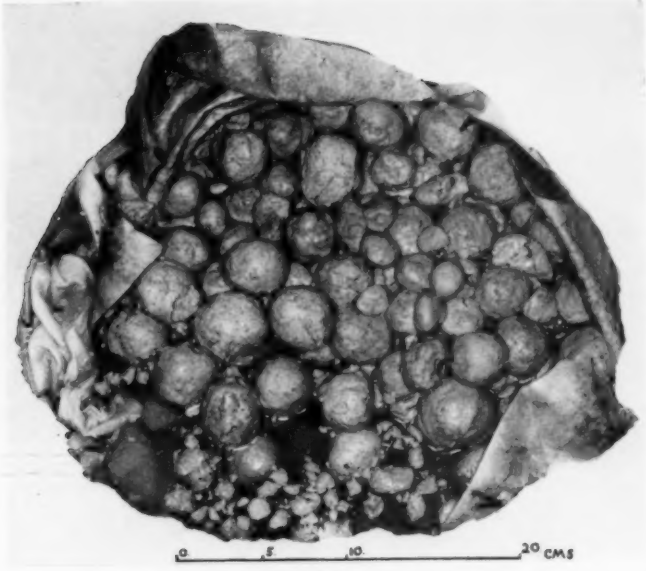

FIG. 1

CAVERNOUS HAEMANGIOMA IN A POST-PARTUM UTERUS

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INTRODUCTION

VASCULAR tumours of the uterus in general are relatively uncommon and endometrial haemangiomata particularly so. A recent comprehensive review by Pedowitz *et al.* (1955) lists 42 cases of haemangioma of the uterus from the literature, all of which were submucous.

This paper reports a cavernous haemangioma of the endometrium found at autopsy in a woman dying in the puerperium from a primary neoplasm of the liver.

CASE REPORT

Mrs. F.R., a 37-year-old Jamaican of African descent, was first seen as an out-patient at the University College Hospital on 2nd November, 1959. She presented with pain in the right hypochondrium of 24-hours duration. She had never been seriously ill before. At the time, she was in the 33rd week of pregnancy, having had 6 successful deliveries and 2 abortions previously. During her last pregnancy (which culminated in a 7-month stillbirth) she had experienced pains of a similar type.

On examination, no obstetrical complications and no abnormality in the abdomen or elsewhere were found. She returned home and on 26th December, 1959 had spontaneous delivery of a living child.

Five days later, she again attended the Casualty Department, complaining that her abdominal pains were more severe, and that her abdomen and ankles were gradually swelling. In addition, she stated that she had noticed profuse vaginal bleeding since delivery.

Examination showed an afebrile, well-nourished woman with lactating breasts, who did not appear acutely ill. Her mucous membranes were somewhat pale, but there was no icterus or lymphadenopathy. She had no cutaneous naevi. Moderate ankle oedema was found.

The abdomen was distended and contained free fluid. The liver was firm and palpable 8 cm. below the right costal margin. She was markedly tender below the left costal margin rendering examination very difficult. Her vaginal bleeding was not considered excessive. Apart from a blood pressure of 130/100 mm. Hg, the rest of the physical examination revealed no abnormality.

The laboratory findings were: Haemoglobin 10·5 g./100 ml.; white cell count 7,000/cu.mm., with normal differential count; serum bilirubin (mg./100 ml.): 1 minute 0·7, total 1·3; plasma proteins (g./100 ml.): total 7·1, albumin 3·3, globulin 3·8; cholinesterase 0·5 Michel units; thymol turbidity 0·4 units; alkaline phosphatase 17 King-Armstrong units.

She was admitted to a medical ward on 1st January, 1960, with a diagnosis of cirrhosis of the liver. On 3rd January, 1960, she vomited once. The following morning she complained of pain "all over the body" and became shocked. The mucosae were extremely pale and her abdomen now became markedly distended.

Paracentesis abdominis was performed and pure blood obtained. She was resuscitated with 6 pints of blood until the evening, when she suddenly collapsed and died.

AUTOPSY REPORT

The pertinent findings were: The body was that of a well-nourished, slightly obese woman with bilateral ankle oedema. The breasts were lactating. The abdominal cavity contained 4½ litres of blood and clots. The liver was grossly enlarged, weighing 5,150 g., and was of a light brown colour; the surface was adherent to the peritoneum on the right side and irregular, due to numerous yellow tumour deposits of various sizes. The edge was irregular and rounded. The capsule was very fragile and burst in several places while the autopsy was being performed, releasing pinkish-grey, necrotic material, and obscuring the source of the ante-mortem haemorrhage. On section, there was a huge "mother tumour" in the right lobe. Much of the parenchyma was replaced by innumerable secondary deposits, many necrotic and haemorrhagic. There was no evidence of a pre-existing cirrhosis. Fragments of necrotic tumour were found in the main branches of the portal vein. Numerous rounded yellow metastases were present in both lungs.

The other finding of unusual interest was in the uterus, which was of a size and consistency in keeping with the date of parturition. The cervix was bruised and patulous. On sectioning the body of the uterus, a raised plaque of tissue (8 cm. in diameter and 1·5 cm. thick) was seen on the endometrial surface posteriorly (Figs. 1 and 2). It was a dark purple colour and appeared vascular. The myometrium was only involved superficially. The ovaries, Fallopian tubes and vagina were normal.

Histology

Liver. This showed a well-differentiated hepatocellular carcinoma with trabecular formation and the characteristic capillary stroma (Fig. 3). There were areas of haemorrhage and necrosis in the tumour deposits. There was fat in both the normal liver parenchyma and also in tumour cells.

Lungs. The metastatic deposits were well differentiated, showing the features of the parent tumour.

Uterus. This showed a cavernous haemangioma involving the superficial myometrium and the endometrium (Figs. 4 and 5). Other sections taken remote from the haemangiomatous tissue showed a thickened myometrium undergoing involutionary changes.

Conclusions. Death was due to intraperitoneal haemorrhage from a rupture of the liver capsule overlying a necrotic focus of tumour. The cavernous haemangioma of the uterus appears to have developed at or near the placental site.

Discussion

Periodically, over the past 30 years, reviews of haemangioma and other vascular tumours of the uterus have appeared in the literature (Horgan, 1930; Marsh, 1950; Macdonald, 1950; Lukić, 1954).

It would be unnecessarily repetitive to list cases reported in previous papers. For those interested in details, the review by Pedowitz *et al.* (1955) is very complete, and contains a most useful bibliography. In addition, their classification differentiates the haemangioma quite clearly from other vascular tumours of the uterus. This is important as there have been conflicts of nomenclature in the past (Gerbie *et al.*, 1955).

The classification proposed by Pedowitz and his colleagues is as follows:

Benign Vascular Tumours (*Angiomas*)

Blood-vessel origin:

(1) Haemangioma:
  Capillary haemangioma
  Cavernous haemangioma
  Haemangiomatosis
(2) Angiomyoma
(3) Haemangioendothelioma (benign)
(4) Haemangiopericytoma (benign)

Lymph-vessel origin:

(1) Lymphangioma
(2) Lymphangiocystic fibroma

Malignant Vascular Tumours (*Angiosarcomas*)

Blood-vessel origin:

(1) Haemangioendothelioma (malignant)
(2) Haemangiopericytoma (malignant)
(3) Kaposi's sarcoma (no cases involving uterus have been reported)

Lymph-vessel origin:

(1) Lymphangiosarcoma

Various theories have been advanced as to the origin of uterine haemangiomata. Whether they are true vascular tumours or hamartomas is still debated (Pedowitz *et al.*, 1955). Klob (1864), reported a case of "cavernous ectasia of the uterus", and theorized that the tumour arose from placental site tissue which failed to undergo involution synchronously with the rest of the uterus. This concept was rejected by subsequent writers on the grounds that haemangioma of the uterus occurs in nulliparous women as well (Marsh, 1950; Pedowitz *et al.*, 1955).

Meyer (1925) thought that pregnancy accelerated the growth of an existing tumour particularly if it was near the placental site. Ritchie and Giles (1955) pointed out that care must be exercised in differentiating between vessels persisting at the placental site and those of true angioma. This has been carefully considered in studying the present case. Figure 6 shows the usual picture in the placental site,

FIG. 1

Uterus and upper vagina opened anteriorly showing dark raised plaque 8 cm. in diameter and 1·5 cm. thick on the endometrial surface posteriorly.

FIG. 2

Haemangioma of endometrium (sectioned after fixation).

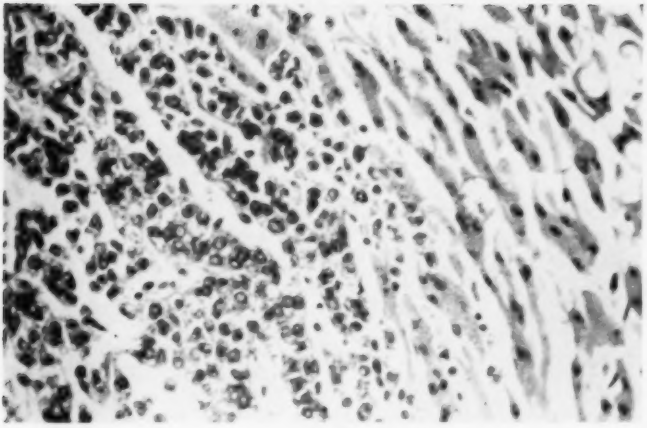

FIG. 3

Hepatocellular carcinoma with trabecular formation and capillary stroma. H. & E. ×368.

FIG. 4

Cavernous haemangioma involving endometrium. H. & E. ×19.

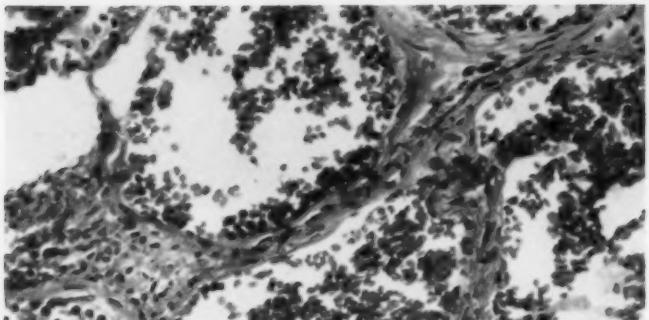

FIG. 5

Detail of cavernous haemangioma of endometrium. H. & E. ×208.

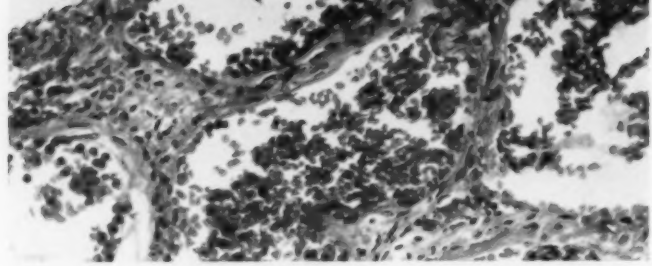

FIG. 6

Normal placental site (biopsy) showing myometrium, decidua and trophoblastic cells. H. & E. ×49.

and may be compared with Figures 4 and 5. Here, there is a profusion of cavernous blood vessels with relatively scanty connective tissue stroma. Only a few fragments of degenerating decidua are present on the surface. By contrast, in material obtained from the normal placental site by the technique described by Dixon and Robertson (1958), the decidual tissue and myometrium is interspersed between the arteries, veins and sinusoids. There are involutionary changes especially in veins and sinusoids with intimal hyperplasia and organizing thrombi.

Oestrogen retention, which occurs in severe liver disease and is said to cause spider naevi (Bean, 1943), might have been a factor in accentuating the growth of the angioma in this case. However, this would be purely hypothetical as there were no spider naevi, liver palms or other evidence of this phenomenon.

Haemangioma of the uterus occurs most frequently during the years of reproductive activity and especially among parous women (Lukić, 1954). However, one must be cautious in attaching significance to the effects of parity as the majority of women have children. Further, it is reasonable to assume that a uterine haemangioma would most likely become symptomatic during the years of endometrial periodicity. In the present case, Mrs. F.R. had 6 successful pregnancies and 2 abortions. If the haemangioma was congenital, it apparently had little ill effect on gestation, although her lochia after this last delivery was unusually heavy.

Why is this tumour rare? It is possible that small haemangiomata may occur in the endometrium more frequently than is generally thought. Ritchie and Giles (1955) presented 10 cases in which angiomatous tissue was identified in the endometrium in 4,385 curettings examined over a period of 6 years. They point out that many such haemangiomata, being superficial, may be shed with the menstrual debris.

Because of its relative rarity, the uterine haemangioma is of little clinical significance. However, it should be considered in the differential diagnosis of uterine haemorrhage. Further, as Malpas and Brundret (1952) stress, it may be an unexpected cause of violent haemorrhage after curettage.

Summary

A case of haemangioma of the uterus in a 37-year old woman who died of intraperitoneal haemorrhage from a massive primary liver-cell carcinoma is presented. The relationship of the haemangioma with the placental site and pregnancy is discussed.

Acknowledgments

I am grateful to Dr. K. L. Stuart of the Department of Medicine, University College Hospital, under whose care the patient was admitted, for permission to use the clinical data.

My thanks are also due to Mr. Riley of the Photographic Unit and Mr. C. Williams for preparation of numerous sections.

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THE DIAGNOSTIC VALUE OF ROUTINE HYSTEROGRAPHY IN CASES OF METRORRHAGIA

BY

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HYSTEROGRAPHY is essential in the diagnosis of metrorrhagia. This is particularly true when dealing with apparently normal uteri.

Marshak *et al.* (1950), Davids (1953), Liliequist (1953) and others have pointed out the high rate of misleading results obtained by diagnostic curettage in cases of metrorrhagia. We are able to confirm these views from the present study of 96 routine hysterographies in cases of meno-metrorrhagia of more than 3-months duration. We have selected 96 consecutive cases of metrorrhagia in whom no pathology was revealed on diagnostic curettage and who did not respond to therapy. The results of this study further confirm the importance of routine hysterography, also in cases where curettage gave indication of some pathology.

MATERIAL AND METHOD

A group of 96 patients has been selected for study with the following criteria: (*a*) Meno-metrorrhagia of at least 3-months duration, resistant to therapy; (*b*) apparently normal-sized uterus on examination; (*c*) no pathology on diagnostic curettage.

Hysterography was performed under direct fluoroscopy employing 1·5–3 c.cm. of contrast medium. In most cases we employed 40 per cent lipiodol. In 11 cases of persistent uterine bleeding actually present during the hysterography the medium used was water-soluble. One oblique and at least three antero-posterior hysterograms were performed in each case. In some cases one film was taken after cannula withdrawal.

RESULTS

The results of hysterograms are summarized in Table I.

TABLE I

Results of Hysterography in 96 Cases of Metrorrhagia in Apparently Normal Uteri

	No. of Cases	Per cent
Submucous and intramural fibroids ..	29	28
Polyps, endometrial	4	4
Adenomyosis	8	8
Cystic glandular hyperplasia	12	12
Intra-uterine adhesions	2	2
Congenital anomalies and normal uteri	37	36

As can be seen in this table, 41 cases, or 39 per cent (29 fibroids, 4 endometrial polyps and 8 cases of adenomyosis) were diagnosed on hysterography and missed on diagnostic curettage. The X-ray diagnosis was later confirmed in 12 cases that underwent operation (fibroids 7, adenomyosis 1, endometrial polyps 4). Four illustrations of these cases are reported (see Figs. 1, 2, 3, 4).

FIG. 1

FIG. 2

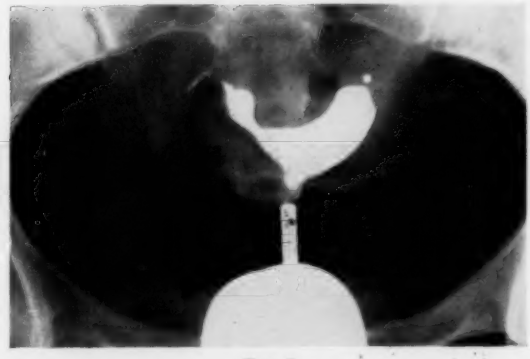

FIG. 3

FIG. 4

S.K., Z.S.

Representative Cases

Case 1 (Fig. 1). B.A., nulliparous, aged 36, had irregular periods of metrorrhagia for twenty years. Treatment consisted in partial resection of ovaries; three diagnostic curettings; X-ray irradiation of ovaries and hypophysis; hormonal therapy; psychoanalytical treatment, all without appreciable improvement.

Hysterogram revealed adenomyosis.

Case 2 (Fig. 2). S.T., aged 49, was gravida-4 and para-2. There had been three years of irregular uterine bleedings. Two curettages revealed non-secretory endometrium with dilated tubules. The uterus was normal sized, retroflexed, with normal adnexa.

Hysterogram, performed after cannula withdrawal, shows a round filling defect with a fine reticular pattern on the submucous fibroid.

Case 3 (Fig. 3). J.Z., was gravida-2 and para-2. There had been heavy bleedings during the menses for one year. Two curettages revealed proliferative endometrium. Hormonal therapy was of no avail.

On hysterography a submucous myoma of the fundus was found. This was confirmed on operation.

Case 4 (Fig. 4). M.A., aged 38, was admitted with severe anaemia (Hb., 6·6 g. per 100 c.cm.; R.B.C., 2,200,000 per c.mm.) due to meno-metrorrhagia. Two previous curettings revealed no pathology. Hysterography confirmed the diagnosis of uterine polyp.

Discussion

The reluctance to use hysterography as a routine diagnostic procedure is due to the fear of complications, namely: infection and extravasation. In this series we have had one case of bilateral salpingitis following hysterography. The past history of this patient revealed an old inflammatory process in the pelvis. Careful check of patient's past history, B.S.R. and blood count, should eliminate such complications.

Extravasation is a rare complication when hysterography is performed under direct fluoroscopy, with small amount of the dye, under controlled pressure and when a short cannula is employed. We had no such complications in this series.

Sweeney reported on many X-ray filling defects which were not confirmed on operation. Such "filling defects" are usually due to uterine contractions, intra-uterine adhesions, secretions, clots, air bubbles, etc. When the diagnosis is in doubt we have usually repeated the hysterography 4–8 weeks later.

Hysterography is naturally no substitute for diagnostic curettage. However, we feel that routine hysterography has a definite place in the diagnosis of meno-metrorrhagia.

Summary

Routine hysterography was employed in the diagnosis of metrorrhagia in apparently normal uteri.

In a group of 96 cases of metrorrhagia, in whom diagnostic curettage revealed no pathology, hysterography disclosed various filling defects in 41 cases (39 per cent).

The routine use of hysterography in cases of metrorrhagia is advocated, also in those patients where diagnostic curettage gives indication of some pathology.

Acknowledgments

We are indebted to Dr. W. Polishuk for his encouragement and guidance in this investigation and we thank the staff of the Rothschild Hospital's Institute of Roentgenology for the facilities granted.

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DIABETES INSIPIDUS AND TOXAEMIA OF PREGNANCY

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DIABETES insipidus is a relatively unusual condition, manifested primarily by polydipsia and polyuria. It is characterized by a disturbance in the regulation of internal fluid balance, which is caused by loss of the antidiuretic principle of the posterior lobe of the pituitary. This hormone acts directly on the distal renal tubules by stimulating the re-absorption of water from the tubular urine.

The lesions producing diabetes insipidus may involve any of the following: supra-optic nuclei, paraventricular nuclei, tuberes nuclei, supra-optico- or paraventriculo-hypophysial tracts, pituitary stalk or neurohypophysis (Williams, 1955).

In a large proportion of cases the disorder appears spontaneously and in the absence of any other demonstrable organic lesion. Not seldom such patients show a family history of diabetes insipidus (Blotner, 1942).

In some patients the syndrome is associated with some lesion affecting the region of the hypothalamus, such as trauma, infection, neoplasm or vascular accident.

In addition to true diabetes insipidus a nephrogenic type is known, which is due to unresponsiveness of the kidney to pituitrin. Wijdeveld, Jansen and Majoor (1959) mention a large number of conditions which can produce nephrogenic diabetes insipidus.

True diabetes insipidus must also be distinguished from psychogenic polydipsia and polyuria. This is possible by the test introduced by Hickey and Hare (1944, *vide infra*).

The prior existence of diabetes insipidus in the female does not appear usually to alter her fertility, the course of her pregnancy, the effectiveness of her labour or her ability to lactate (Hendricks, 1954). However, as the disease occurs infrequently, the combination with pregnancy is understandably rare. To date about 50 cases have been reported.

The co-existence of diabetes insipidus and pregnancy merits more than a casual consideration, inasmuch as there are implications both from the obstetrical and from the endocrine standpoint. Still more interesting problems arise when the syndrome is complicated by severe pre-eclampsia. In the literature little is to be found on this subject (Nash, 1946; Dieckmann, 1952).

CASE REPORT

Mrs. G.S., a 30-year-old gravida-1, was first seen by me in the 25th week of pregnancy.

Past history: Since her 10th year she has taken nasal insufflations of pituitrin powder three times daily to control her polyuria and polydipsia, which had first manifested itself during her infancy. At 3 and 9 years of age she was investigated for these symptoms at the paediatric clinic of the University Hospital at Groningen. According to information obtained from that clinic, she drank at that time 2–3 litres of fluids in addition to the normal hospital diet. The daily urinary output was 3–4 litres. The specific gravity ranged from 1,003 to 1,006 and after dehydration reached a maximum value of 1,012. On X-ray study of the skull no abnormality of the sella turcica was noted. Apart from her polydipsia and polyuria the patient had been well all her life. At school she showed a normal intelligence. The family history was negative for diabetes insipidus.

Her prenatal course had been normal until recently. Her only complaint was that the pituitrin powder seemed to be less effective. During the last weeks she had to take 4 doses daily instead of 3 to control her thirst.

On physical examination the patient was observed to be well developed. She was about 24-weeks pregnant. The uterine fundus measured 1 cm. above the umbilicus. The blood pressure was 125/80. Urinalysis was negative for albumin and sugar. A glucose tolerance test showed

normal values. Blood group: A, rhesus negative. Serology was negative. Pelvic examination showed a slight contraction of the inlet.

At the 32nd week of pregnancy the patient showed excessive weight gain, definite oedema and a slight rise of blood pressure (140/90). There was no albuminuria. Her need for pituitrin had decreased; she took only 2 doses daily. The patient was instructed to reduce her salt intake drastically. Two weeks later her weight and oedema had further increased; the blood pressure was 170/110. The urine contained albumin. The uterus did not seem to have grown much. The patient did not have any complaints; her usual thirst had almost completely disappeared and she now took but one dose of pituitrin daily. Next day she was admitted to the hospital and treatment with bed-rest, sedation and complete salt-restriction was instituted. The administration of pituitrin was discontinued and this was tolerated without a significant increase in urinary output.

Laboratory data. A specimen of urine voided on admission contained 3 g./litre albumin, no sugar and no white or red blood corpuscles. Blood urea: 310 mg./litre; uric acid: 6·4 mg. per cent; creatinin: 1·1 mg. per cent; Na^+: 145 mEq/litre; Cl^+: 109·3 mEq/litre; K^+: 5·1 mEq/litre. The test for anti-Rh antibodies negative.

The urinary output ranged between 1·5 and 2 litres daily, specific gravity between 1,008 and 1,013. Ophthalmological examination failed to show any abnormalities. When the blood pressure after two days of treatment remained at the level of 170/110, oral therapy with protoveratrinum A (Puroverine-retard, Sandoz) was commenced. The first day 2 tablets of 0·3 mg. were given and during the next days the dosage was increased to 6 tablets daily. The blood pressure fell to 150/100, but after some days rose again to 175/110. Addition of intramuscular Puroverine, twice daily 0·1 mg., failed to have any hypotensive response. Blood uric acid rose to 7·5 mg. per cent. Blood electrolytes and blood urea remained stable. Proteinuria continued at a level of 1–2 g./litre.

Pregnancy had now progressed to 35 weeks. Danger of intra-uterine death of the foetus as the result of persisting pre-eclampsia seemed real and it was felt that delivery was necessary. Ten days after the admission to the hospital Caesarean section was performed under cyclopropane anaesthesia. A boy weighing 1,760 g. was delivered; it was mildly asphyxiated, but soon recovered. The placenta contained many infarcts and was small (weight 410 g.). The post-operative course was uneventful. During the first 7 days following delivery the mean urinary output was 2 litres daily, without pituitrin medication. The specific gravity ranged between 1,008 and 1,012. After a week the proteinuria had disappeared and the blood pressure had decreased to 140/100. As the baby was nursed in the incubator lactation was suppressed by the administration of oestrogens. Two and a half weeks after delivery the patient began to suffer from thirst again and once more started to take one dose of pituitrin daily. After 6 months her need for pituitary extract was still much lower than before pregnancy, that is, 1–2 doses daily.

It should be mentioned, that on X-ray study of the skull the sella turcica was found to be rather small.

To ensure that true diabetes insipidus existed a Hickey–Hare test was done, 6 months after delivery. This test is based upon the fact that the rapid introduction of a large volume of hypertonic saline by the intravenous route calls forth a marked antidiuretic response in the normal individual. By preserving water the body tries to defend itself against the sudden upset of the isotonicity of the blood-stream. In true diabetes insipidus, however, no antidiuretic response is obtainable and the orally established diuresis continues unabated.

The procedure, proposed by Carter and Robins (1947), was followed. All antidiuretic therapy was stopped 24 hours prior to the test. Food was permitted, but fluids were forbidden for 8 hours preceding the test; as she suffered from considerable thirst the patient could not carry out this order completely. The patient was then hydrated with water, 20 ml. per kg. of body weight by mouth over a period of one hour. Thirty minutes after the period of hydration was begun an indwelling catheter was inserted. Urine specimens were collected at 15 minute intervals and the urine-flow calculated in ml. per minute. After 2 periods with an adequate urine flow, that is greater than 5 ml. per minute, an intravenous infusion of 500 ml. of 2·5 per cent sodium chloride was started. The hypertonic saline was administered at the rate of 0·25 ml. per kg. of body weight per minute during 45 minutes. Twenty minutes after completion of the infusion 0·1 unit of pituitrin was given intravenously and its effect on urine flow observed. The result of the test is illustrated in Figure 1 and shows a curve typical for diabetes insipidus. The diuresis continues unabated due to the absence of a sufficient antidiuretic response, but decreases markedly after the injection of pituitrin. The curve of a normal subject is shown for comparison.

There are two points in this case history, which merit consideration. In the first place the high degree of insensitivity of the pregnant uterus to pituitrin medication is remarkable. During the first and second trimester of pregnancy the patient took about 70 units of pituitary extract daily by nasal insufflation without any sign of increased uterine contractility. Greene and Gibson (1939) stated that premature labour is frequent in patients with diabetes insipidus, receiving pituitrin medication, but most observers seem to have noted no increase in uterine contractility, or else only mild, irregular contractions.

Much more important is the occurrence of a severe toxaemia and the remarkable changes in polyuria and polydipsia in our case.

In the cases reported a great variability in the effect of pregnancy on diabetes insipidus is found (Blotner and Kunkel, 1942). The disease

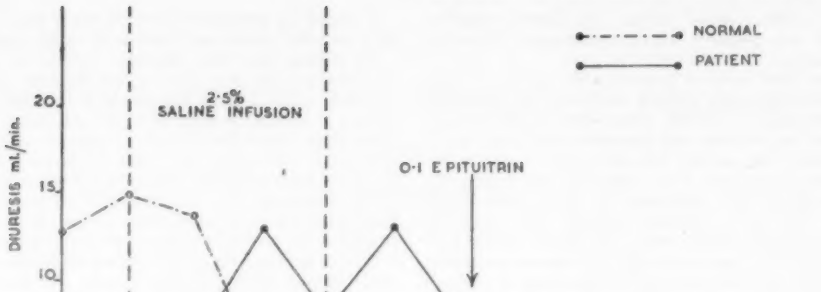

FIG. 1
Hickey–Hare test.

may be aggravated or ameliorated. Several cases have been reported in which the syndrome was uninfluenced by pregnancy. Diabetes insipidus may appear transiently only during pregnancy or persist afterwards. Diabetes insipidus may also appear after delivery.

In our case there was first a period of increased need for pituitrin; in the 8th month of pregnancy however the polyuria and polydipsia disappeared completely, to return slowly after delivery, but in a lesser degree compared to the pre-gravid state. The amelioration in the symptoms of diabetes insipidus took place exactly at the same time and in the same measure as the toxaemia of pregnancy worsened, so that a correlation between these two phenomena is strongly suggested. We are confronted with the question, whether such a correlation really existed and, if so, can it be explained?

From the numerous studies on the renal glomerulo-tubular mechanism during normal and abnormal pregnancy the conclusion can be reached, that almost all investigators are of the opinion, that in pre-eclamptic toxaemia tubular re-absorption of water and electrolytes is increased, while renal plasma flow and glomerular filtration rate decrease (Gevers, 1958). One could be tempted to accept these data as an explanation of the decrease in polyuria and polydipsia at the time of the patient's toxaemia. On closer consideration, however, it is clear that these changes in renal function cannot be the only cause of the observed phenomena, because the symptoms of diabetes insipidus showed a persistent improvement after delivery, whereas renal function in toxaemia soon becomes normal again after termination of pregnancy.

Therefore it is necessary to look for another and more permanent factor to explain the favourable influence on the symptoms of diabetes insipidus. Perhaps the solution of this problem is to be found in the circumstance that the diabetes insipidus in this case was probably incomplete, by which is meant, that the ability of producing antidiuretic hormone was not completely lost. This assumption is based on the fact, that, at the time of the investigation in the paediatric clinic, the specific gravity of the urine reached a maximum value of 1,012. According to Williams (1955) in typical diabetes insipidus the specific gravity does not exceed

1,005. The permanent improvement of the disease after delivery lends in itself further support to the supposition, that some remnant of antidiuretic hormone-producing tissue was left in this patient. It is accepted that such incomplete lesions occur (Hendricks, 1954).

Now it is conceivable that pregnancy had a stimulating effect on the neurohypophysis and/or hypothalamus of our patient, thereby causing a partial restoration of the ability to produce antidiuretic hormone. It is well known that such a stimulation can take place in lesions of the *anterior* pituitary lobe. Sheehan and Murdoch (1938), Murdoch and Govan (1951), Bishop and de Mowbray (1951) reported that Simmonds's disease may subside if the subject succeeds in becoming pregnant again. Why then should not the same thing happen in defects of the posterior lobe or its overlying neural components?

Another possibility was suggested by Dr. Tj. de Bruïne at a meeting of the Dutch Gynaecological Society, in which this case was discussed. He pointed out that the severe pre-eclampsia of our patient could have damaged her liver-function. And, since it is well known that the liver is able to inactivate antidiuretic hormone, it could be supposed that not an increased production, but a decreased inactivation of pituitrin underlies the observed improvement of the disease.

There are, however, some strong arguments than can be brought forward against this assumption. Firstly it must be pointed out that the mechanism of elimination of antidiuretic hormone is not yet completely understood. From different experiments the inference can be drawn, that oxytocin is rapidly metabolized (Berde, 1959). Part of it seems to be excreted in the urine, but most of the circulating hormone would appear to be inactivated in the kidney tissues, as is the case with parenterally-administered vasopressin, which is inactivated by the kidneys and by the organs of the splanchnic vascular area (Ginsburg and Heller, 1953). By *in vitro* studies it has been demonstrated, that not only liver, but also blood, spleen, kidney and other tissues destroy the posterior pituitary hormones (Williams, 1955). How then could liver-damage alone cause a decreased inactivation of these hormones?

Secondly, it is open to question, whether the liver in pre-eclampsia is seriously damaged. Dieckmann, Smitter and Pottinger (1951) found liver-function tests virtually unchanged, apart from slight impairment of bromsulphalein excretion. According to Ingerslev and Teilum (1945) liver-biopsies in pre-eclampsia are normal.

Therefore, it seems difficult to maintain the assumption of a decreased inactivation of antidiuretic hormone as a result of liver damage. On the contrary, the theory of stimulation of the neurohypophysis and/or hypothalamus by pregnancy, resulting in a permanent improvement of function, seems to meet no valid objections, although of course it lacks proof.

Besides an increased production of endogenic pituitrin the aforementioned changes in renal function, which are characteristic for pre-eclampsia, will have aided in decreasing the need for exogenic pituitrin. The disappearance of this influence after delivery makes the partial recurrence of the symptoms of diabetes insipidus understandable.

Another phenomenon, which if possible must be clarified, is the increased need for pituitrin during the 6th and 7th month of pregnancy. In 1930 von Fekete found that the serum from pregnant women was able to inactivate oxytocin. Since then this finding has been confirmed by numerous investigators. According to Page (1946) the inactivation is probably caused by an enzyme, which he called pitocinase and which he thought was produced by the placenta. McCartney, Vollach and Pottinger (1952) showed that the inactivating substance was absent in the first weeks of pregnancy, could be demonstrated in varying degree between the 10th and 18th week and was always present after the 18th week of pregnancy. Page (1946) and Dicker and Whyley (1959) found, in keeping with other investigators, that the oxytocin inactivating ability of serum and plasma of pregnant women increases with the duration of pregnancy up to the 36th week. After that time it remains unchanged. The power of inactivation of plasma by a woman in labour is such, that 2·0 ml. of plasma incubated *in vitro* with oxytocin inactivates more than 5 units of the drug in 10 minutes. The inactivation not only affects the oxytocic activity of posterior pituitary

extracts, but also the antidiuretic effect, as demonstrated by Dieckmann, Egenholf, Morley and Pottinger (1950). Although the part played by pitocinase in the physiology of pregnancy is as yet only partially known, the aforementioned data could give an explanation of the increased need for pituitrin of our patient during the 6th and 7th months of pregnancy, for at that time her blood must have contained enough oxytocin-inactivating substance to diminish perceptibly the antidiuretic effect of the administered pituitrin.

Assuming that oxytocinase is produced exclusively by the placenta—which does not seem to be an established fact—one could further put the question, whether changes in the secretion of this enzyme could not have had a part in the disappearance of the symptoms of diabetes insipidus at the time of severe pre-eclampsia. It could be supposed, that the production of oxytocinase by the placenta decreased as a result of the toxaemic damage in this organ. In this case the pituitrin produced by the stimulated neurohypophysis would be inactivated in a lesser degree and thus have more effect.

It is very much open to question, however, whether one can follow this line of reasoning, because only extremely small amounts of enzyme are required to bring about an enzymic process. Woodbury, Ahlquist, Abren, Torpin and Watson (1946), Page (1946), Aragon (1948) and McCartney, Vollach and Pottinger (1952) found no significant differences between the pitocinase activity in serum of normal and toxaemic pregnant women. Although a decrease in pitocinase activity in the blood of our patient cannot be excluded for certain, there seems to be no reason to attribute great importance to this eventuality.

On the possible influence of the foetal pituitary on the maternal diabetes insipidus we need not speculate at great length. The fact that the polyuria and polydipsia did not return immediately after delivery argues strongly against this.

Finally, the course of the diabetes insipidus after pregnancy must be considered. It is remarkable, that the cessation of placental activity did not have a perceptible influence on the diuresis. This indicates that substances of placental origin did not take an important part in the temporary disappearance of the symptoms of diabetes insipidus. Only some weeks after delivery a slight degree of polydipsia recurred, which led to the resumption of pituitary medication.

The explanation of this recurrence seems obvious. The changes in renal function, caused by the pre-eclampsia, had gradually disappeared and no longer made their antidiuretic effect felt. As a result of this the insufficiency of the neurohypophysis became manifest again. Nevertheless the favourable influence of pregnancy on the pituitrin producing tissues seems to have been permanent, because the patient now needs much less pituitary medication than before her pregnancy.

It seems we are permitted to draw the following conclusions from this case history:

(1) Pre-eclampsia can occur in spite of the absence of a normally functioning neurohypophysis.

(2) The hormones of the neurohypophysis do not seem to play an important part in the pathogenesis of pre-eclamptic toxaemia.

(3) Pregnancy appears to have—at least in certain circumstances—a stimulating influence on the pituitrin producing tissues in neurohypophysis and hypothalamus.

Summary

The case of a patient suffering from diabetes insipidus, who became pregnant and developed a severe pre-eclampsia, is reported.

During the last months of pregnancy remarkable changes in the intensity of the polyuria and polydipsia occurred. After delivery by Caesarean section at the 36th week the diabetes insipidus showed a permanent improvement. An explanation of these phenomena is sought for.

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REPORTS OF SOCIETIES

SOUTH WESTERN OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

October 1960

A meeting of the Society was held at Odstock Hospital, Salisbury, on Saturday, 29th October, 1960, with the President, Mr. Nicholson-Lailey, in the Chair.

The meeting was opened by Mr. J. G. Reynolds, who presented a paper on

Some Aspects of Uterine Cancer

He reviewed a series of fifty-six cases of uterine body cancer occurring between 1955 and 1959, believed to represent a total incidence of this disease in a mainly rural area with a population of 130,000. The ratio of uterine body cancer to that of cervix had been found to be 1·24 : 1 in the four years, 1955–1958. He stressed the high incidence of the disease between fifty to fifty-five, the age when irregular menstruation is often attributed to the menopause and led to delays in diagnosis for up to two years. Nine out of the eleven deaths so far encountered have occurred in patients with a history of disease for one or more years before treatment.

Surgical removal of the growth was completed in fifty out of the fifty-five (one patient had been brought in dead). Total hysterectomy, with bilateral salpingo-oöphorectomy, was done thirty times, extended total hysterectomy fifteen times, Wertheim's operation three, and sub-total twice. Radiotherapy had been used only for recurrences and when extension of growth had been found in the pelvis at operation. Extension of growth into the cervix was found in 27 per cent but recurrences after operation were not more common in these cases. Eight out of nine of the pelvic recurrences found, occurred within six months of operation. Deep X-ray therapy, especially cesium, has been found effective in treating secondary growth; only one has died and no palpable tumour could afterwards be found in all but one. In this case the disease appears to have been arrested for three years. Ovarian secondaries were found in five cases, and all have survived up to four years with no sign of recurrence. The cervix was left unsutured in many cases before operation, though latterly it has been blocked with gauze. One case of vault recurrence was observed in the fifty cases, and this after the cervix had been blocked.

The suggestion was made that a five- and ten-year follow-up should be presented with cases under the age of sixty when first seen. This would give better indication of the curability ratio than inclusion of elder patients, who may be more liable to die from old age or of recurrent disease.

Mr. J. N. Barron illustrated a paper on

Some Congenital Abnormalities and Their Management

with colour slides.

He described a method of constructing an artificial vagina and considered the treatment of many of the congenital defects of the newborn, including epispadias, lymphangiomata, many different types of naevi and congenital defects of the limbs.

Meningomyelocele is a not uncommon occurrence which should be treated as an urgent problem. Many of these defects can be closed by wide mobilization of the surrounding tissues, without the need for secondary skin grafting. Harelip should be closed at about the third month, and the cleft palate at the age of one year. Half the cases require a second operation before school age to achieve a good cosmetic result. Palatal closure is sometimes delayed for years where there is a wide anterior defect. Speech Therapists, the School Dental Service and Orthodontists assist in achieving good physical results but the ultimate fate of the patient depends on the attitude of the parents and family. Where this is unsatisfactory, inferiority tendencies may lead to a wide range of psychological disturbances.

Congenital constriction bands of the toes, fingers and limbs sometimes require urgent early incision or simple Z plasty if distal ischaemia is to be prevented.

The results of treating hypospadias by current methods are unsatisfactory. Two new methods, one experimental and unpublished, and the second described by Cecil in the U.S.A. are being used in an attempt to reduce the complication of fistula which occurs in about 50 per cent of cases operated upon.

In the discussion which followed the use of chymotrypsin was discussed and its use in gynaecological surgery. In plastic surgery, Mr. J. M. Barron thought it was effective in some cases but not absolutely reliable. Mr. J. J. Foley had been impressed when using it on 25 patients having pelvic floor repair operations.

Professor Jeffcoate read a paper on

Dyspareunia Following Vaginal Operations

(This is reported on page 1 of the February issue of *The Journal of Obstetrics and Gynaecology of the British Commonwealth*)

Mr. T. N. MacGregor described a method of Z plasty for relieving the vaginal constriction which sometimes occurs following vaginal operations, and had also abandoned the posterior wall repair as a routine procedure in operations to repair uterine prolapse.

In answer to questions Professor Jeffcoate stated that one of his criteria for vaginal hysterectomy in cases of prolapse in the absence of some other indication, was the presence of a small uterus where both the utero-vesical and rectovaginal peritoneal pouches were low in position.

Dr. G. L. Foss reviewed the history and literature connected with the Stein-Leventhal Syndrome.

He believes this condition to be a well-defined syndrome with infertility, amenorrhoea, oligomenorrhoea or menometrorrhagia as presenting symptoms, and hirsuties and obesity as occasional findings. The histories and findings in 11 cases were presented and the paper was illustrated with photographs of the patients, the operation findings and histology of the ovarian biopsies, with particular reference to the presence of arteriolar sclerosis, clusters of primordial follicles beneath the thickened capsule, and hyperplasia and luteinization of cells of the theca interna.

Dr. Foss stressed the value of pneumoperitonography as an aid to diagnosis of enlarged ovaries, but pointed out that at times the diagnosis is only confirmed when the ovaries are actually incised.

Dr. K. T. Evans and Mr. E. M. Edwards presented a demonstration of

Ovarian Enlargement by Means of Gynaecography

The investigation is not a new one, but it is one which is little practised, although pneumoperitoneum was first used in X-ray diagnosis by Weber as long ago as 1912.

There are two methods in use in Bristol. The first is the transabdominal route, whereby 1 litre of carbon dioxide is introduced into the peritoneal cavity by paracentesis, and the patient tilted to the head-down position to allow the gas to accumulate in the pelvis. The second method is particularly applicable to married women complaining of infertility, and is of particular interest in suspected cases of the Stein-Leventhal syndrome; it combines tubal insufflation with hysterosalpingography. Using Sharman's insufflation apparatus carbon dioxide is passed into the uterine cavity at the rate of 60 ml. per minute for 15 minutes, with the patient lying prone in the head-down position. Following this, aqueous contrast medium is injected, using 7–10 ml. of Diaginol viscous. Radiographs are then taken in rapid succession, whilst the patient is still tilted at 40 degrees to the horizontal; two films are used, giving each a different exposure to allow a margin for error.

The main difficulties in the trans-uterine method are the result of spasm; this can be minimized by giving pre-medication with pethidine, and by giving inhalation of octyl nitrite. Naturally, tubal occlusion is an absolute bar to its success, and in such cases resort is made to paracentesis.

The main advantage of the trans-uterine method is that the one investigation provides information concerning ovarian sizes, and at the same time allows the Fallopian tubes and uterine cavity to be visualized.

There were no complications in the cases in this series.

Dr. N. R. Butler and Mr. M. R. Fell described three cases of

Ovarian Neoplasm in Children

The first was a child aged five, who presented with vaginal bleeding and breast development, and on examination was found to have a faint growth of pubic hair, but otherwise normal external genitalia. Rectal examination revealed a cystic pelvic mass the size of a walnut.

Laparotomy was performed and the right ovary was found to contain a simple follicular cyst but otherwise the pelvic organs were normal and the adrenals were palpated and no abnormality was found. The cystic ovary was removed. Histological examination showed no neoplasia. Radiological bone age was within normal limits and other investigations, including X-ray of skull, vaginal smear, urinary ketosteroids, all proved normal.

The eventual diagnosis was true precocious puberty of pituitary origin associated with a non-neoplastic ovarian cyst. This child has been followed up subsequently and has been well. The mammary development has regressed.

The second case was a child, aged eight, who presented with a short history of abdominal swelling and intermittent right-sided abdominal pain. On examination the abdomen was found to be enormously enlarged by a cystic mass, and there were signs of early sexual precocity, viz., pubic hair, slight mammary enlargement and pigmentation of nipples. Laparotomy revealed a tumour the size of a football arising from the left ovary. This tumour was partly solid and partly cystic and there was a much smaller tumour the size of a cherry in the right ovary. Palpation of the supra-renals, kidneys, liver, stomach, para-aortic lymphatics and uterus revealed nothing else abnormal. The left ovary was removed and the smaller tumour on the right ovary enucleated. Post-operative histological examination of these tumours showed the bigger one to be a malignant teratoma and the smaller an apparently benign teratoma.

The child was followed up as an out-patient, and the secondary sexual characteristics became less marked, though her radiological bone age was definitely advanced. She remained well for a year but then developed secondaries and subsequently died. Post-mortem showed numerous metastases from the ovarian carcinoma.

The third child was a school girl, aged fourteen, referred with an abdominal tumour and irregular periods. Her periods commenced at the age of eleven years and had been regular until shortly before first attending. There was a large firm mass arising out of the

pelvis the size of an eighteen-week pregnancy. She was *virgo intacta* and it was thought the mass was an ovarian tumour.

A laparotomy revealed a solid mass arising from the right ovary the size of a large melon. The mass was slightly adherent to the posterior parietal peritoneum and the pouch of Douglas. The left tube and ovary and the uterus looked normal and there were no palpable glands or secondary deposits elsewhere. After mobilization this mass was removed with conservation of the uterus and left appendage, following which she made a good recovery and has subsequently remained well and symptom free. Histologically the mass appeared to be a malignant teratoma with possible dysgerminoma in some parts. This girl's radiological bone age is extremely advanced, but to date she is making good progress.

SIXTEENTH BRITISH CONGRESS OF OBSTETRICS AND GYNAECOLOGY

THE 16th British Congress will be held in Bristol on 16th, 17th and 18th July, 1962. The programme will include a symposium on "The Blood in Pregnancy". Other subjects to be discussed are "Embryogenesis and its Environment", "Dermatology of the Vulva", "Treatment of Endometriosis" and "Post-operative Care and Complications of Prolapse Repair Operations".

Communications relating to this Congress should be addressed to: The Hon. Secretaries, British Congress of Obstetrics and Gynaecology, University Department of Obstetrics, Southmead Hospital, Bristol, England.

BOOK REVIEWS

"Obstetrical and Gynaecological Pathology for Postgraduate Students." By R. E. REWELL, M.D., M.R.C.P., Consultant Pathologist, United Liverpool Hospitals. Pp. xii+435, with 150 figures. E. & S. Livingstone, Edinburgh and London, 1960. Price 50*s*.

DR. REWELL has made a brave attempt to fill a notable gap among British textbooks. He has succeeded in projecting his personality as well as his views, drawing on his considerable experience not only in Britain but also in India, not only in hospitals but also in zoos. One consequence of this variety of background is that his book abounds in what the *New Yorker* calls "incidental intelligence", e.g., that Swiss-cheese endometrium means nothing to the Indian medical student who has never seen any variety of cheese; or that fibroids are rare in nulliparous monkeys.

The gynaecological pathology is naturally described predominantly in terms of histology, and indeed only one of the more than 100 illustrations in this section is other than a photomicrograph. The histogenesis of ovarian tumours and the pathology of uterine malignancies are particularly well discussed, and there is a useful chapter on cytology and smear techniques.

Dr. Rewell is to be commended on devoting fully one-third of his text to obstetrical pathology. In this field he has taken a wider view of his brief and has included much clinical material. This is evidenced by such chapter headings as infertility studies, anaemia in pregnancy, toxaemias, defects in blood clotting, maternal mortality and morbidity, perinatal pathology and congenital abnormalities. In many of these the author ranges beyond pathology to prophylaxis and treatment.

The postgraduate with examiners still to face will find this a valuable book, but he would probably prefer the inclusion of more detailed discussion of such *viva* "hardy annuals" as the pathogenesis of red degeneration, the relationship between kraurosis and leukoplakia vulvae, and Spiegelberg's criteria of ovarian pregnancy. References are more than adequate and remarkably up to date, but there are a few surprising omissions, such as Claude Taylor's paper on mixed mesodermal tumours of the uterus. The index is sketchy, occasionally inaccurate and altogether unworthy of the book it concludes.

In summary, Dr. Rewell has been bold in conception if somewhat uneven in execution. No doubt a second edition will soon be called for, when it is to be hoped that any revision and supplementation of the text will not be at the expense of the pervasion of the book by the author's personality.

"From Girlhood to Womanhood." By ALBERT SHARMAN, M.D., D.Sc., F.R.C.O.G. Pp. 72, with illustrations. E. & S. Livingstone, Edinburgh and London, 1960. Price 6*s*.

THIS is an admirable little book for those teenage girls and their mothers who have a high enough standard of intelligence and education to enable them to cope with the somewhat laboured style of its writing.

"Medical and Biological Research in Israel." Edited by M. PRYWES. Pp. 563, with illustrations. Hebrew University, Jerusalem, 1960. Price $8.

THIS is a justly proud survey of research carried out in Israel during the first 12 years of its nationhood. It should serve as an inspiration to other emergent states, although the latter are unlikely to possess to the same degree the material advantages that accrued and the trained professional workers who gravitated to Israel when independence was attained.

Among those of international standing whose work is summarized are Gurevitch in genetics, Serr Sachs and Danon in the prenatal determination of sex, Shelesnyak in embryology, the Zondeks in endocrinology, Halbrecht in gynaecological tuberculosis and Joel in seminology.

"A Short Textbook of Midwifery." By G. F. GIBBERD, M.B., M.S., F.R.C.S., F.R.C.O.G. Seventh edition. Pp. viii+582, with 197 figures. J. & A. Churchill Ltd., London, 1960. Price 36*s*.

A NEW edition of such a popular textbook for students is always welcome, and in the latest "Gibberd" many improvements and minor modifications have been made.

The section on hyperemesis gravidarum has been extensively revised and the view that in the past many severe cases with jaundice were, in fact, infective hepatitis, has been accepted. The emphasis on fluid and electrolyte balance in therapy is in line with current opinion. The importance of cervical incompetence is stressed and its treatment now described; here one meets the only spelling error to be found—that of Shirodkar.

In view of the excellent results obtained by Pedersen and others, the section on diabetes and pregnancy would be improved by mentioning the value of control by blood sugar levels rather than by urine testing. Vartan's classic work on the aetiology of breech presentation is ignored and the relative safety of extended legs as compared with the footling is not mentioned. Following a full consideration of ante-partum haemorrhage, the syndrome of hypofibrinogenaemia is only briefly described.

It is a pity that, after the lucidly written sections on normal labour and the third stage, the student is left with the impression that a moderate blood loss is normal after delivery. The importance of ergometrine as a first

item in the management of post-partum haemorrhage is wisely emphasized, although not yet advised as a prophylactic measure to reduce the blood loss and morbidity of the normal third stage.

The notable chapter on puerperal infections has been wisely retained, but it has been revised and yet further improved by a discussion of the changes which have been brought about by the present rising importance of *Staphylococcus pyogenes* in hospital infection. With corresponding changes in the section on sulphonamide and antibiotic therapy this chapter remains unsurpassed.

A well-balanced section on Obstetrical Anaesthesia has been added which deals fully with the maternal dangers and how they may be prevented. An adequate description is given of the technique of percutaneous pudendal block. For forceps delivery, despite this excellent comment on anaesthesia, gas, oxygen and ether are advised; while the classical forceps technique, using the whole hand in the vagina, is still advocated, no mention being made of the restricted two-finger technique that has become almost universal in conjunction with pudendal block. Similarly, Kielland's forceps, which students see frequently used these days for many rotational deliveries, are not mentioned. The description of the Walcher position to aid a high forceps when section is too dangerous is clearly out of place. Another technique which might well be eliminated in the next edition is the detailed description of Braxton Hicks bi-polar version.

Despite these minor criticisms of detail, the author's "Midwifery" will remain a classic contribution by one who has done so much to improve obstetric practice in this country.

"Carcinoma *in Situ* of the Uterine Cervix." By GILBERT H. FRIEDELL, M.D., ARTHUR T. HERTIG, M.D., and PAUL A. YOUNGE, M.D. Pp. viii+154. Illustrated. Blackwell Scientific Publications, Ltd., 1960. Price £3.

THE concept of "carcinoma *in situ*" originated at the beginning of this century and is still under discussion by clinicians as well as morbid anatomists. Although by now the fact that malignant growth undergoes a pre-invasive stage has been more or less generally accepted, there is still great controversy among pathologists with regard to its diagnostic criteria. It is a disturbing fact that tissue sections which one pathologist may confidently regard as "carcinoma *in situ*" may be labelled by other pathologists, equally confidently, as "chronic cervicitis" at the one extreme and "frankly invasive carcinoma" at the other.

The monograph by Friedell, Hertig and Younge, concerned with a detailed study of 235 cases of *in situ* carcinoma of the cervix uteri collected from the material of the Free Hospital for Women (Boston, Mass.), will greatly contribute to the clarification of the subject. All relevant problems in diagnosis and management are discussed with admirable precision and paucity of words. Since, as the authors emphasize in their epilogue: "the carcinoma *in situ* problem requires the co-ordinated efforts of the clinician, the cytologist and the pathologist," this book was written by two clinicians and one pathologist and contains a special chapter on the cytology of the lesion written by a cytologist. Not only are the histological findings reported and illustrated in great detail, but an excellent attempt at grading carcinoma *in situ* according to the degree of histological differentiation is also made. Borderline cases at either end of the scale, i.e., benign epithelial hyperplasia and carcinoma *in situ* with questionable early stromal invasion are discussed from every aspect and it is shown convincingly that serial sectioning of all the material available is essential for establishing the correct diagnosis. The clinical findings in these cases according to age, marital state, racial incidence, symptoms, general appearance of the cervix and location of the lesion are discussed. Adequate space is devoted to clinical aids such as the Schiller test and exfoliative cytology with a critical review of the diagnostic potential of the methods. Colposcopy is mentioned but, regrettably, not elaborated owing to lack of experience with this technique. The chapter on management of the disease and critical evaluation of therapeutic results is of particular interest. The authors conclude that each patient represents an individual problem and stress the fact that unnecessary radical therapy may be as tragic as too much conservatism. The experienced gynaecologist will correlate the choice of treatment with the clinical and histological appearance of the lesion. This volume contributes much to the achievement of this aim.

Erica Wachtel

"Resuscitation of the Newborn Infant." Edited by H. ABRAMSON. Pp. 274, with 36 figures. C. V. Mosby, St. Louis; Henry Kimpton, London, 1960. Price 75*s*.

CAN we afford to have a doctor present at every delivery? Can we afford not to? Do we give sufficient training in skilled resuscitation of the newborn? Should we not adopt the Apgar or some similar method of scoring the condition of the baby at birth, so that we could compare statistics, and more easily assess any depressant effect on the foetus of a drug administered to the mother? Is it not time we abandoned intragastric oxygen as ineffective and time-wasting? These are some of the questions which come to the mind, and perhaps to the discomfit, of the British reader of this transatlantic book. The 24 contributors, who come from laboratory and clinical fields, are members of the Special Committee on Infant Mortality of the Medical Society of the County of New York.

A very broad view is taken of the antecedents of foetal loss, and factors are considered which might be operative not only before labour but even before pregnancy. Yet gaps in our knowledge are freely admitted and the lack of agreed definitions is deplored. The seventeen chapters include a masterly summary of salient points in physiology and biochemistry, to which are appended no less than 124 references. The obstetrician will appreciate all 17, but the consecutive chapters entitled "The

First Sixty Seconds of Life" and "Resuscitation Procedures in the Delivery Room" merit the close attention of all who in any professional capacity attend women in labour.

A few statements and quotations will elevate the British eyebrow, e.g., that 12 hours is now generally considered in most clinics the dividing line between normal and prolonged labour; or that 50 per cent of multiple pregnancies are not diagnosed until the time of delivery. But overall this is a balanced account, and on points where no final judgment is made, such as the optimum time to ligate the cord, or the merit of slow delivery of the foetal trunk, the arguments for and against a procedure are presented fairly.

This book deserves reading by everyone who practises obstetrics and a place in every obstetric library. Its practical message can be reinforced by seeing the film, in colour and with sound track, of the same title, which the authors sponsored.* The price of this book is not too high for the value of its contents, which include extensive references, a glossary, an author index and a subject index.

S. Bender

* Obtainable on free loan from Smith, Kline & French Laboratories, Welwyn Garden City, Herts.

DONALD AND FOTHERGILL MEETING

to be held at

SAINT MARY'S HOSPITALS, WHITWORTH PARK, MANCHESTER

on

FRIDAY, 7TH JULY, 1961

FURTHER to the notice in the February issue requesting visitors who intend to be present at this meeting to signify this intention before the end of March, it is recognized that in many cases this may not be possible. It will facilitate the arrangements if prospective visitors will inform Dr. K. V. Bailey as soon as possible.

REVIEW OF CURRENT LITERATURE

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PREGNANCY

56. **The Basal Temperature Curve in Pregnancy.** (La curva de la temperatura basal en la mujer embarazada.)

By M. Cusí. *Rev. españ. Obstet. Ginec.*, **19**, 132–136. May–June, 1960. 7 charts.

The author states that in spite of the numerous references in the literature to the basal temperature curve in normal and pathological menstrual cycles, and the variations resulting from hormonal treatment, very little attention seems to have been given to its appearance during pregnancy. He was able to discover only four articles dealing with this subject since 1948. He reviews three of these articles as follows:

Buxton and Atkinson (*J. clin. Endocrin.*, 1948, **8**, 544) observed that the basal temperature (BT) was elevated during the first three months of pregnancy and then dropped to reach the preovulatory level by the fifth month. Klein (*Geburtsh. u. Frauenheilk.*, 1951, **11**, 418) stated that after the first three months of pregnancy a drop occurred which did not respond to large doses of progesterone. Siegler and Siegler (*Fertil. and Steril.*, 1951, **2**, 287) described their results in 1,012 graphs, and confirmed the fall in basal temperature during the fourth month. They observed no alterations in the curve with the approach of labour. Because of the scarcity of observations that have been made during pregnancy the author decided to study the problem in 7 of his own patients.

He observed the BT during the first 5 to 7 months of pregnancy. All the patients had been under treatment for infertility and had taken their temperatures for at least two months prior to becoming pregnant. The rectal temperature was taken every morning before rising. If they had been out of bed during the previous five hours, had less than the normal number of hours of sleep, had sexual intercourse or any alteration in their normal state of health, this was carefully noted. Stilbenes and vitamin E were administered to 5 of the patients, and 2 of them also received oestradiol benzoate. Another patient had been taking vitamins E and T constantly and also 10 mg. of progesterone daily at the time of the missed periods. The last patient had no treatment whatsoever. Blood oestrogen estimations and 48-hour estimations of urinary pregnandiol excretion were performed on the 2 patients who received oestradiol.

The authors found that the BT reached its maximum during the first six weeks of pregnancy in 6 out of the 7 patients. In the other patient it did so in the third month. The BT began to drop during the second half of the second month in 6 patients. The drop seemed to be accentuated after each missed period. The preovulatory level of the BT was reached during the fifth month in one patient, at the end of the sixth month in 2 patients, and in the remaining 4 patients it had not been reached after 6 months.

This investigation shows that in general the BT does not maintain an even plateau during the first 3 months of pregnancy, but on the contrary it rises to reach a

maximum before the sixth week, when it begins to drop. The author did not confirm previous observations that the preovulatory level of the BT was reached at the fifth month. The majority of these patients had not reached that level by the sixth or even the seventh month.

When oestrogens were administered there was no drop in the BT. In fact the drop was even more noticeable when this form of medication was discontinued. Similarly, when progesterone was injected there was no rise in the BT at the time of the injections, but a slight rise occurred a few days after they were discontinued after the fourth and fifth missed periods. "In the pregnant woman the action of oestrogens and progesterone on the BT is the reverse of what it would be in the non-pregnant woman."

The author attempts to explain this paradox. In experiments as yet unpublished he has noticed that the injection of 20 mg. of progesterone intravenously for two days in pregnant women with a deficient pregnandiol excretion only produced a rise of 1–2 mg. in the amount of pregnandiol excreted. Conversely, the administration of oestrogens to these cases was followed by a rapid increase in excretion of pregnandiol, signifying a greater secretion of progesterone by either the corpus luteum of pregnancy or the placenta. It is to be expected, therefore, that administration of oestrogens during early pregnancy will not cause a drop in the BT, but may even cause it to rise.

Nevertheless, a time will arrive when progesterone has no effect upon the BT during pregnancy. This is demonstrated by two observations: (1) Klein showed that the injection of enormous doses of progesterone produces no elevation of the BT after it has dropped; (2) the author's graphs show that the BT drops even after the amount of endogenous progesterone has increased, as demonstrated by a marked rise in the pregnandiol excretion. The latter observation not only confirms the previous observations of Klein, but demonstrates the lack of correlation between the secretion of progesterone and the BT. It may also compel us to revise the hypothesis that elevation of the temperature follows ovulation and the formation of the corpus luteum.

D. G. Wilson Clyne

57. **Studies in Blood Oestrogen Levels in Pregnancy.** (Untersuchungen über den Blut-Östrogenspiegel in der Gravidität.)

By G. Ittrich, A. Jakobovitz and H. Igel. *Zbl. Gynäk.*, **82**, 1772–1774. Nov. 12, 1960. 2 tables. 6 refs.

The oestrogen concentration in the blood of 26 pregnant women was estimated. In 3 other women determinations were carried out before the onset of labour as well as early and late during the first stage. The level of total oestrogens rises from 2·7 μg. during the third month to 11·5 μg. per 100 ml. prior to the onset of labour. During the first stage of labour the concentration rises to 18·2 μg. per 100 ml.

From the authors' summary

58. **Free Lysine Excretion in Pregnancy.**

By J. H. Bolton, F. M. C. Forster and L. F. Kerley. *Lancet*, **2**, 345–346. Aug. 13, 1960. 1 table. 1 fig. 8 refs.

Of all the free amino acids excreted in the urine during pregnancy the greatest variation is shown by lysine. Because of its stability it is more likely to reflect changes in protein utilization than other amino acids.

Thirty-one pregnant patients were studied by means of monthly examinations of a 24-hour specimen of urine for lysine content. Of the patients studied, 11 had a normal pregnancy, 9 developed pre-eclampsia and 3 showed evidence of placental insufficiency. The daily lysine excretion of the pregnant patients was greater than in 15 non-pregnant controls. In general there was a gradual rise in excretion to a maximum at about 3 months followed by a gradual fall to delivery. The highest levels of excretion were found in the cases of placental insufficiency and the lowest in the normal pregnancies. The differences in the three groups were apparent at an early stage in pregnancy and the relative levels in excretion were maintained throughout. The results obtained suggest that increased lysine excretion may be related to certain pregnancy diseases. If this finding is confirmed by further investigations it may prove to be of considerable clinical value because any change from normal is apparent early on in the pregnancy.

J. M. Brudenell

59. **Use of Hydrochlorothiazide (Esidrix) in Pregnancy.**

By H. E. Schmitz, M. P. MacLaverty and R. S. Pavlic. *West. J. Surg. Obstet. Gynec.*, **68**, 290–293. Sept.–Oct. 1960. 19 refs.

Sixty patients with oedema and 60 patients with pre-eclampsia were given a 1,200-calorie low-salt high-protein diet, with a minimum of 3 litres of fluid a day and also 50 mg. of Esdrix twice daily. If this did not produce a diuresis the dosage was increased to 100 mg. twice daily. Patients were kept on this regimen until delivery or until a positive salt and water balance was noted; treatment varied from 3 days to 16 weeks with an average of 24 days. A control group of 60 patients with oedema were kept on the dietary regimen, but were not given any medication.

It was found that long-acting tablets were not successful and 7 patients had a sudden increase in oedema in spite of a good diuresis, these responded to intermittent dosage with 5 days' medication followed by 2 days' rest. Most of the pre-eclamptic patients had a drop in blood pressure (they had all been admitted to hospital) and the serum sodium did not change, although there was a marked fall in the serum chloride. The serum potassium remained unchanged. Slight weakness, dizziness and nausea occurred in 7 patients but cleared up without medication and without interruption of the hydrochlorothiazide.

The authors conclude that the drug is an effective agent in the management of oedema and pre-eclampsia.

D. C. A. Bevis

60. **Guanethidine: a New Antihypertensive Substance of Use in Obstetrics and Gynaecology.** (La guanetidina: una nuova sostanza antiipertensiva applicata in ostetricia e ginecology.)

By L. D'Incerti Bonini. *Ann. Ostet. Ginec.*, **82**, 855. Aug. 1960. 21 refs.

The new synthetic substance Guanethidine (2-(octhydro-l'azocinil)-ethyl-guanidine) has been found to have a powerful anti-hypertensive effect. Its action is apparently due to sympatheticoplegia.

It has been successfully used in gynaecological and obstetric cases where hypertension exists. It may be given by mouth in doses of 20 to 40 mg. daily or parenterally in doses of 10 to 20 mg. daily.

The drug has a constant hypotensive effect with remarkably few side effects. It tends to cause a slight rise in serum potassium and a fall in nitrogen. Used alone, or in combination with modern diuretics it is very useful in toxaemia of pregnancy. Once the blood pressure has fallen, a low maintenance dose is all that is required.

Josephine Barnes

61. **Listeriosis and a Possible Cause of Abortion.**

By F. K. Oehlschlager. *Obstet. and Gynec.*, **16**, 595–600. Nov. 1960. 4 figs. 17 refs.

A case is reported of neonatal death due to sepsis. There was mild bronchopneumonia, early abscesses of the liver, spleen, bowel and adrenal glands, and meningitis. All involved areas and blood culture grew *Listeria monocytogenes*. The same organism was grown from the mother's vagina. She had had 2 previous abortions, possibly also due to the infection. Following treatment with terramycin, the patient had a successful pregnancy.

The organism is known to produce abortion and septicaemia in animals. It has been isolated from man, although the symptoms it produces are few and non-specific. There is some evidence that transplacental infection which originates in the vagina is a rare cause of foetal septicaemia.

J. G. Dumoulin

62. **Myocardial Infarction During Pregnancy and the Puerperium.**

By H. Watson, D. Emslie-Smith, J. Herring and I. G. W. Hill. *Lancet*, **2**, 523–525. Sept. 3, 1960. 2 tables. 2 figs. 38 refs.

Only 26 authentic cases of myocardial infarction during pregnancy and the puerperium have been described. Two further cases seen in the department of Medicine and Obstetrics in the University of St. Andrew's at Dundee are presented. The patients were aged 22 and 17 years; neither had severe anaemia, hypertension, diabetes mellitus or other metabolic disorder. The elder patient had an anterior transmural myocardial infarct at 38 weeks. She recovered with rest and was delivered at term by Caesarean section so as to avoid the strain of labour. Her puerperium was uneventful and she has since had a further pregnancy, this time culminating uneventfully in a normal delivery. The younger patient had a posterior myocardial infarct three days after delivery. The diagnosis was not made until a week later when a fortuitous electrocardiogram showed the pattern of a recent posterior infarct. This provided an explanation for an attack of chest pain three days post-partum which had originally been considered to be abdominal in origin. The patient made an uneventful recovery, being treated with rest and sedation.

The authors point out that the changed lipid pattern in pregnancy resembles that found in men with ischaemic heart disease. This occurs in spite of the fact that oestrogens when used therapeutically are effective in restoring the so-called non-atherosclerotic pattern. The rarity of coronary disease in pregnancy implies that if the changed lipid pattern is related to atherosclerosis or thrombosis some mechanism must operate during pregnancy to protect the woman from her "atherogenic" lipid pattern. The fact that there seems to be no correlation between the time at which the reported cases of infarction have occurred in pregnancy and the changes in circulating lipid (which are maximal at about the 33rd week) argues in favour of other aetiological factors. The majority of the previously reported cases have occurred in older patients, 36 years or over, many of them with arterial hypertension. There was no correlation between either the age or blood pressure and the duration of pregnancy at which infarction took place in these patients. In the younger patients, however, infarction almost invariably occurred late in pregnancy. It is of interest that most patients who survived their infarcts did well. In some of the recently reported cases anticoagulant therapy has been used without ill effects even immediately after delivery.

J. M. Brudenell

63. **Anticonvulsants as a Factor in Megaloblastic Anaemia in Pregnancy.**

By P. B. B. Gatenby. *Lancet*, **2**, 1004–1005. Nov. 5, 1960. 2 tables. 8 refs.

Some of the anticonvulsant drugs used in the treatment of epilepsy may cause megaloblastic anaemia. Their chemical structure resembles that of folic acid and it has been suggested that the anaemia results from an interference with folic acid metabolism. The author studied the incidence of megaloblastic anaemia in 70 pregnancies occurring in 44 epileptics who attended the Rotunda Hospital, Dublin, during the years 1953 to 1958 inclusive. In 13 pregnancies no anticonvulsant treatment was given at all; one case of megaloblastic anaemia occurred in this group. In 48 pregnancies the patients received phenobarbitone alone; no cases of megaloblastic anaemia were seen amongst these patients, but in 7 pregnancies where phenytoin was combined with phenobarbitone there were 3 confirmed cases of megaloblastic anaemia. In each case a rapid cure was effected by the administration of folic acid by mouth, in spite of continued anticonvulsant therapy. It is concluded that patients receiving phenytoin together with phenobarbitone in pregnancy should be either given folic acid prophylactically or else observed carefully during the latter part of pregnancy for evidence of megaloblastic anaemia.

J. M. Brudenell

64. **Sickle-cell Disease in Pregnancy.**

By M. Anderson, L. N. Went, J. E. MacIver and H. G. Desion. *Lancet*, **2**, 516–521. Sept. 3, 1960. 4 tables. 31 refs.

The authors report 17 cases of sickle-cell disease in pregnancy among patients attending University College Hospital, Jamaica. Nine of the 17 had sickle-cell anaemia, 7 had sickle-cell/haemoglobin C disease and one an unusual mixture of a sickle-cell gene with a thalassaemia-like gene. Differentiation between the various types of the disease was made by haemoglobin electrophoresis. The most striking complications in sickle-cell disease are the acute episodes. Pregnancy appears to precipitate these and they were seen in 8 of the 9 patients with sickle-cell anaemia. In two cases the exacerbations occurred only in the puerperium. By contrast, the clinical manifestations of the disease were not striking in the sickle-cell/haemoglobin C cases. It would seem that pregnancy does not materially affect the natural history of the latter condition. No serious maternal complications were seen in any of the 7 cases in the series.

The foetal prognosis in sickle-cell disease is usually stated to be bad. The cause for this is unknown but a crisis may bring about intra-uterine death or the onset of premature labour. In the present series there was only one intra-uterine death associated with an episode of severe anaemia. None of the cases of sickle-cell/haemoglobin C showed any foetal complications but the average birth weight of the infants both in this group and the sickle-cell anaemia group was less than average.

From the point of view of management patients with sickle-cell disease in pregnancy are best treated conservatively. Frequent visits to the antenatal clinic, an adequate diet and admission to hospital a few weeks before delivery are recommended. During a crisis the patient should be confined to bed in hospital. Antibiotics may be indicated in cases of infection but blood transfusion is only indicated where the haemoglobin level falls below 6·0 g. per 100 ml. None of the drugs thus far advocated in the treatment of the disease seemed to produce any significant effect. Delivery does not present any special difficulties and premature induction and Caesarean section should only be performed when indicated on obstetric grounds.

In discussing the incidence and inheritance of sickle-cell disease in Jamaica the authors state that the condition occurs as frequently in pregnant women as in the general population. Although this may in part be due to the recent increased efficiency in diagnosing the condition it does seem that Jamaican women with sickle-cell disease have a greater chance of survival to the age of reproduction than their counterparts in other areas of the world.

[The fact that the maternal and foetal hazards are less serious than in previous published reports is of interest to obstetricians practising in the British Isles where an increasing number of cases of sickle-cell disease in pregnancy are being seen as a result of large-scale immigration from the West Indies.]

J. M. Brudenell

65. **Studies of the Passage of Constituents of Foetal Blood Through the Placenta.** (Untersuchungen zur Plazentapassage fetaler Blutelemente.)

By G. Oehlert, J. E. Mohrmann and C. F. Michel. *Zbl. Gynäk.*, **82**, 1544–1551. Oct. 1, 1960. 33 refs.

The question is discussed whether the Rhesus antigen is only linked to foetal red blood corpuscles, or whether it can also be demonstrated in the placenta. The authors believe that as regards the antigen-antibody reaction the placenta is a neutral organ and that it is not responsible for the formation of maternal antibodies. They studied the passage of foetal blood into the maternal circulation using chemical and microscopic methods.

The average contents of foetal haemoglobin (HbF) in retro-placental blood was 6·79 per cent. In 29 out of 93 cases examined, however, there was a marked increase in this value up to a maximum of 59·9 per cent. Eleven patients whose retro-placental blood contained a high proportion of HbF, also showed a high level in the mother's venous blood, taking 0·5 to 0·7 per cent of HbF as the normal range in pregnant women and in adults generally. In Rh-negative women with Rh-antibodies an average of 13·7 per cent of foetal Hb was found in the retro-placental blood, which is twice the figure found in the other cases in the series.

The HbF in the venous blood of 63 patients was studied at various stages of pregnancy and in 35 patients examination was carried out during and after delivery. There was a marked rise in the proportion of HbF in labour which subsided during the puerperium.

The authors conclude that high HbF values are due to the passage of foetal blood into the maternal circulation and into the retro-placental blood. They consider that this is responsible for the formation of maternal antibodies and that not a few cases of death of the foetus during labour or shortly afterwards may be due to loss of foetal blood by this route.

Bruce Eton

66. **Prediabetes and Pregnancy.** (Prediabetes y gestacion.)

By J. A. Clavero Núñez, E. Hurtado, F. Llamazares and J. Botella Llusiá. *Rev. espan. Obstet. Ginec.*, **19**, 16–21, Jan.–Feb. 1960. 1 table. 15 refs.

The authors describe 24 cases of habitual foetal death. In a previous investigation in the Provincial Institute of Obstetrics and Gynaecology, Madrid, Caballero and Hurtado discovered 17 cases of habitual foetal death which they thought were due to unsuspected diabetes because of (*a*) previous family history of diabetes or suspected diabetes, (*b*) previous history of stillbirths without known cause, usually with large infants, (*c*) the finding of hyaline membrane or hyperplasia of the islets of Langerhans in these infants at autopsy.

In their present investigation the authors have excluded all cases of habitual foetal death associated with (*a*) cervical insufficiency, (*b*) uterine fibroids, (*c*) arcuate or septate uterus, (*d*) perinatal haemorrhagic disease, (*e*) syphilis and (*f*) dystocia. On the other hand they included all habitual foetal deaths of unknown aetiology, as well as those associated with hypermature foetuses and

prolonged gestation. They did not include any cases (with one exception) in which foetal death occurred before the 24th week of pregnancy.

All the patients were given 8 units of protamine insulin daily at breakfast time, the dose being increased by 1 unit weekly according to tolerance, until 14 to 16 units were being given daily. Treatment began at the second month, and was carried on throughout the whole of pregnancy. Only two cases showed hypoglycaemia which required the administration of glucose at the same time as the insulin injection. Eighteen of the patients also received 10 to 40 mg. of oestrogens daily, 14 received special diet especially when they were obese, and 3 were given thyroid extract also.

Prior to receiving this treatment the 24 patients had produced 7 live infants in 103 pregnancies, a foetal mortality of 92 per cent. The same patients, with insulin therapy, produced 19 live babies in 24 pregnancies, a success rate of 79 per cent. *D. G. Wilson Clyne*

67. **A Critical Analysis of the Management of Pregnancy in Diabetic Women.**

By H. McLendon and J. R. Bottomy. *Amer. J. Obstet. Gynec.*, **80**, 641–652. Oct. 1960. 17 tables. 13 refs.

This is a study of 170 pregnancies, 4 of which produced twins, in 106 diabetics from 1949 to 1957 inclusive. Sixteen of the pregnancies ended in abortion (foetus less than 500 g.). The incidence of congenital malformations was 1 per cent and of hydramnios 5 per cent. Toxaemia, not including chronic hypertension, occurred in 13 per cent. compared with a general incidence in the clinic of 7 per cent. The total foetal wastage, not corrected for abortions or congenital malformations, was 33·4 per cent. Large infants (over 4,500 g.) caused a high incidence of shoulder dystocia. Caesarean section was done in 16 per cent and in 17 per cent labour was induced at the end of 37 weeks. Fifty of the patients received oral stilboestrol therapy "as outlined by Smith and Smith", but there was no significant decrease in the incidence of toxaemia in those patients so treated. There were 6 neonatal deaths presumably in the first 28 days.

F. J. Browne

68. **Smoking during Pregnancy.** (Fisiopatologia de la gestante fumadora.)

By G. Rodriguez Lopez. *Rev. espaň. Obstet. Ginec.*, **19**, 230–248. Sept.–Oct. 1960. 82 refs.

This article deals exhaustively with the social and psychological problems of smoking during pregnancy, including the pharmacology of tobacco and its effects on the genital tract, respiratory system, circulatory system, and endocrine system, and the outcome of pregnancy.

D. G. Wilson Clyne

69. **Bacterial Shock in Obstetrics and Gynecology.**

By R. H. Adams and J. A. Pritchard. *Obstet. and Gynec.*, **16**, 387–397. Oct. 1960. 24 refs.

The commonest causes of bacterial shock in obstetrics and gynaecology are infections from the urinary or genital tract or from transfusion of infected blood. Gram-negative bacteria which release endotoxins are the usual organisms. The authors have experience of 15 cases, 9 of which had pyelonephritis, 8 of them associated with pregnancy.

Clinical features include infection, hypotension and oliguria. After tests to detect the organism, broad-spectrum antibiotics should be promptly started, and these can be changed if necessary when the organism has been detected. An intravenous drip of nor-adrenalin (Levophed) is used to combat the hypotension. It may have to be continued for several days and can produce complications such as thrombosis and tissue necrosis. Aramine may be a better pressor agent in oliguric cases as it can be given intramuscularly. Hydrocortisone seems to do no harm and may do some good, so it can also be given. *J. G. Dumoulin*

70. **The Pathogenesis of Utero-Placental Apoplexy.** (Ueber die Entstehung der uteroplazentaren Apoplexie.)

By F. Kiss and G. Tarján. *Zbl. Gynäk.*, **82**, 1757–1772. Nov. 12, 1960. 8 figs. 59 refs.

The authors carried out anatomical studies of the distribution of blood vessels in the wall of the uterus, with the particular object of throwing some light on the pathogenesis of utero-placental apoplexy.

They describe a "subperitoneal plexus" of blood vessels which contains tortuous large and small arteries derived from the myometrium, as well as large and small veins in great numbers, connected to the arteries by anastomotic bridges. This plexus extends downwards as far as the utero-vesical peritoneal reflection in front and the utero-sacral ligaments in the back. Close examination shows that the larger veins are accompanied by a mass of capillaries which communicate not only with the vein from which they derive, but also with neighbouring veins. The superficial part of the plexus contains a number of sinuses. The tortuous arteries derived from the myometrium have a radial arrangement.

The authors believe that this subperitoneal plexus is of importance in a number of clinical conditions and functions as a mechanical buffer. In cases of uterine hypoplasia premenstrual pain is attributed to stasis in the plexus and the subsidence of the pain is due to resumption of normal blood flow with the onset of menstruation.

During labour the contracting uterine muscle expresses blood in two directions and part of it into the plexus. When the uterus relaxes the circulation is restored. In cases of uterine atony the placenta fails to separate in the third stage of labour because the blood circulating in the sub-peritoneal plexus prevents an adequate rise in intra-vascular pressure in the intervillous spaces.

The authors describe areas of thickening in the wall of uterine arterioles which have a sphincteric action, capable of regulating the local blood flow. If the vascular wall is damaged the small blood vessels may not be able to withstand excessive changes in intra-vascular pressure such as is seen in utero-placental apoplexy. The result is

rupture of the vessels, with sub-capsular and sub-peritoneal haematomata and haemorrhages in the myometrium. If the plexus is unable to take up the displaced blood it may accumulate in the inter-villous space and result in placental detachment.

Bruce Eton

LABOUR

71. **Childbirth with a Large Foetus: A Deductive Study Based upon 4,000 Cases.** (Consideraciones en torno al parto del feto grande. Estudio deductive sobre 4,000 casos.)

By J. Esteban y Altirriva and J. M. Francés Tutasaus. *Rev. españ. Obstet. Ginec.*, **19**, 26–39. Jan.–Feb. 1960. 17 tables. 38 refs.

In this investigation a foetus of over 4,000 g. (8·8 pounds) is taken as a "large foetus". There were 464 large foetuses according to this definition in 3,914 deliveries (11·9 per cent). The authors give numerous tables and conclude that:

1. Large foetuses are relatively more frequent in multiparae.
2. The size of the parents influences the size of the foetus.
3. Excessive foetal size can cause disproportion with a pelvis of normal size.
4. The average duration of pregnancy was 291 days.
5. The average foetal length was 52 cm. (20·8 inches).
6. The majority of the foetuses presented by the head.
7. The duration of labour was not affected, provided that it was well conducted.
8. The incidence of obstetric operations, and their type, was not noticeably different.
9. Too much emphasis has been placed on the size of the foetal trunk as a cause of dystocia.
10. Episiotomy should be practised liberally in these cases.
11. The abnormally large gestation sac seldom causes atonic postpartum haemorrhage.

D. G. Wilson Clyne

72. **Induction of Labour by Digital Separation of the Lower Pole of the Amniotic Sac.** (Inducción del parto por el despegamiento digital del polo inferior del huevo.)

By J. M. Trincado Dopereiro. *Rev. españ. Obstet. Ginec.*, **19**, 166–176. July–Aug. 1960. 8 tables. 33 refs.

The first part of this paper is devoted to a discussion of the various factors which are thought to control the onset of labour, including (1) Maturation of the contractile system of the myometrium; (2) The formation of the lower segment; (3) The softening and relaxation of the cervical plug; (4) The formation of the bag of waters; (5) The destruction of decidual cells with the liberation locally of oxytocic substances such as choline, acetylcholine and histamine; (6) The alteration of the enormous and active interchange between the maternal fluids and the amniotic fluid, leading to a progressive increase in amniotic volume, (7) Friction by the separated membranes exerted upon the internal os, thus stimulating the cervical plexus and causing reflex stimulation of the pituitary gland and hypothalamus.

The author then enumerates the reasons for induction of labour by separation of the membranes, and lists the essential pre-requisites for success, namely: (1) Braxton-Hicks contractions occurring 2–3 times every 20 minutes; (2) Sufficient development of the lower segment, as demonstrated by engagement of the head; (3) A mature cervix, that is to say: (*a*) In primigravidae the cervix must be soft, succulent, of the same consistency as the lower segment, completely effaced, one inch thick at its lower extremity and sufficiently dilated to allow the easy passage of the finger; (*b*) In multiparae the cervix may be effaced or not, the only essential being its softness and its permeability to the finger. The technique of separation is also described, the membranes being stripped from their attachment to the lower segment for at least 2·5 cm. from the internal os.

The author's material included 167 primigravidae and 249 multiparae. Of these, 64 were 4–17 days premature; 158 were at term and 194 were 4–18 days or more post-mature by their calculated dates.

Labour began within 12 hours in 12·2 per cent; between 12 and 24 hours in 44·6 per cent; between 24 and 48 hours in 23·5 per cent; between 48 and 72 hours in 11·0 per cent; between 72 hours and the 6th day in 4·2 per cent. The interval was unknown in about 3 per cent. Expressing the results rather differently, in Group I were 89 primigravidae and 45 multiparae whose pregnancy had lasted under 280 days, whereas in Group II there were 78 primigravidae and 204 multiparae whose pregnancies exceeded 280 days. The successes in these four classes were 84·2, 82·2, 94·8 and 95·5 per cent respectively.

Labour was normal in 381 cases; forceps delivery—perineal or low mid-forceps—was performed in 21; Caesarean section was employed in 3 cases and in 11 the method of delivery was unknown. 394 infants were born alive and survived; and there were 8 antepartum, 1 intrapartum and 4 postpartum infant deaths. The 8 antepartum foetal deaths were due to conditions which were not connected with the method of induction.

The author compares these results with those obtained in 51 women whose pregnancy exceeded 280 days, by simple vaginal examination combined with the introduction of the finger into the cervical os. As only 56 per cent went into labour within 72 hours he concludes that separation of the membranes from the lower segment must have been responsible for the success obtained in the former group.

D. G. Wilson Clyne

73. **Choice of Mode of Delivery in Patients with Heart Disease.** (Wahl des Entbindungsverfahrens bei Herzfehlern.)

By H. Luft. *Zbl. Gynäk.*, **82**, 1329–1334. Aug. 27, 1960. 2 tables. 27 refs.

Amongst 17,934 patients seen during the years 1955–1959 cardiac disease in pregnancy occurred in 1·7 per cent. A rise in the incidence during the individual years

is attributed to improved diagnostic methods. 78 per cent of the cardiac cases suffered from mitral disease and one of the patients died.

In the management of labour the author used a pharmacological block of the autonomic nervous system on the grounds that a reduction of the basal metabolism would reduce the circulatory requirements. In cases of cardiac insufficiency prior to the onset of labour "Prothrazin" (promezathine) and "Dolcontral" (carboxypiperidine) in a proportion of 1 : 2 were administered. After delivery treatment was continued with a lytic cocktail: "Prothrazin", "Dolcontral", and "Propaphenin" (chlorpromazine).

Similar treatment was carried out in cases of operative delivery. As pethidine passes the placental barrier after 40 minutes, the drugs blocking the autonomic nervous system were only given 15 to 30 minutes before the operation.

The author secured satisfactory results by instituting a special antenatal clinic for cardiac disease in close co-operation with a cardiologist.

Bruce Eton

74. **The Administration of Intravenous Oxytocic Drugs Together with Pentothal in Normal and Pathological Labour.** (L'association de la perfusion d'ocytocique à l'anesthésie au pentothal dans l'accouchement normal et pathologique.)

By P. Guilhem, A. Pontonnier, R. Baux, M. Monroziès, P. Armengau, G. Espagno and P. Bennet. *Gynéc. et Obstét.*, **59**, 173–186. 1960. 4 refs.

The authors working in a maternity department in Toulouse point out that in 4,000 deliveries preparation for labour by psychoprophylaxis was successful in the majority of cases. However, in 650 (170 of which are reported in abstract No. 80) because of pain or dystocia, heavy analgesia or anaesthesia was indicated.

They found indications, too, for speeding up labour by the use of oxytocic drugs and have combined the two treatments in that they give drip transfusions containing 10 units of Syntocinon per litre and small doses of 2·5 per cent Pentothal sufficient only to induce unconsciousness. They give repeated small doses of Pentothal into the drip. They have everything ready to intubate the patients, should this be necessary. They claim that labour is speeded up remarkably and that in spite of the artificiality of the process, delivery in a multiparous patient can often be spontaneous, although in a primigravid woman it must always be by forceps. They state that in the 650 cases they have not had to resuscitate more babies than they would have with any other treatment and that with rare exceptions the babies cry immediately.

They only had 5 perinatal deaths in the 650 deliveries, two due to congenital malformation, one premature baby with cerebral haemorrhage, one baby weighing 6 pounds also with cerebral haemorrhage and one breech delivery with asphyxia.

They make the point that this kind of "directed" labour can only be carried out in a fully-equipped unit where laboratories and consultant obstetricians are available.

Elliot E. Philipp

75. **The Action of Potassium on the Excitability of the Uterus in Pregnancy.** (L'action du potassium sur l'excitabilité de l'utérus pendant la grossesse.)

By V. D. Petrescu, A. Haulica and M. Pavelescu-Mincu. *Gynéc. et Obstét.*, **59**, 335–345. 1960. 16 figs. 14 refs.

The authors investigated the action of potassium on the isolated uterus of pregnant and non-pregnant rats and guinea-pigs, using chemically pure potassium chloride. A preliminary investigation showed that potassium in the bath in which the uterus was placed increased spontaneous contractions and could intensify them until tetany was produced. Furthermore, potassium potentiated the action of oxytocic drugs.

With these laboratory findings in mind, they carried out experiments on 9 patients, in 5 of them administering KCl intravenously and in 4 cases by mouth. When the KCl was administered by mouth, it took 2 to 3 days for the uterus to reach its maximum excitability as determined by the Lorand tocograph.

Electrical messurements showed that intravenous injection of 2·5 milligrams of KCl provoked a contraction which lasted 4 to 5 minutes. It had its maximum intensity of 300 mV between 1½–3 minutes after the beginning of the injection. In a second case, similar but less high readings were obtained.

Observations were made, too, on the action of KCl intravenously after 0·001 of a unit of Syntocinon had been administered.

The authors consider that the action of KCl given after artificial rupture of the membranes is superior to that of oestrogens in potentiating natural oxytocic action, that it is similarly superior to oestrogens in overcoming inertia, and that when it is administered with Syntocinon in intravenous transfusions it enables a lower dose of Syntocinon to be used with increased likelihood of a rhythmic uterine action.

Elliot E. Philipp

76. **A Changing Trend in Complications at the Pelvic Brim Demonstrated in X-ray Films.** (Gestaltwandel der Beckeneingangskomplikationen, aufgezeigt durch das Röntgenbild.)

By R. Frischkorn. *Zbl. Gynäk.*, **82**, 1577–1581. 8 Oct. 1960. 3 tables. 1 fig. 13 refs.

The author believes that the pelvic deformities causing cephalo-pelvic disproportion have changed during the last few decades. He considers that in many cases in which there is difficulty at the pelvic brim, the occiput is in a central anterior or posterior position and the cause is not adequately investigated. He carried out postpartum radiological examination of 185 patients in whom this complication had arisen. A narrow pelvis was found in 24 cases and a "long" pelvis in 74 (35 per cent).

Cases of "long" pelvis were classified into 3 groups: (1) Partial assimilation of the 5th lumbar vertebra with the sacrum; (2) Complete assimilation of the 5th lumbar vertebra giving rise to a sacrum with 6 pieces, but without loss of the sacral concavity; (3) Complete assimilation

of the 5th lumbar vertebra with a straight sacrum. The last variation causes a steep angle of inclination of the pelvic brim, as in the previous group, but in addition the available space in the pelvis is reduced owing to failure of development of the sacral curve. All types of assimilation tend to increase the true conjugate, which may exceed the transverse diameter of the brim. The author believes that this abnormality is responsible for a high central anterior or posterior position of the occiput.

Twenty-seven of the 74 patients with a "long" pelvis had a spontaneous delivery (36·5 per cent) and 47 (63·5 per cent) required operative assistance. More than half the patients with a "long" pelvis, namely 39, showed as the main complication a high head with a central anterior or posterior position of the occiput.

Bruce Eton

77. **A Technique for Recording Foetal E.C.G. During Labour and Delivery.**

By C. A. Hunter, K. G. Lansford, S. B. Knoebel and R. J. Braunlin. *Obstet. and Gynec.*, **16**, 567–570. Nov. 1960. 6 figs.

This paper reports a technique for recording the isolated foetal electrocardiogram during labour and delivery. The membranes had to be ruptured and the cervix at least 3 cm. dilated. An electrode which had spring steel wires with sharpened points was fixed to the foetal scalp; a similar electrode was fixed to the maternal perineum. The leads from these were fed into a pre-amplifier, and various apparatus was used [beyond the abstracter's ability to describe] which eliminated the maternal E.C.G. and attenuated voltage artifacts.

J. G. Dumoulin

78. **The Conservative Treatment of Uterine Rupture.** (El tratamiento conservador de las roturas uterinas.)

By R. G. Valenzuela and R. R. Madariaga. *Rev. españ. Obstet. Ginec.*, **19**, 105–114. May–June 1960. 8 charts. 33 refs.

The authors survey the opinions of authorities in North and South America and elsewhere on the treatment of choice for rupture of the uterus, and they quote statistics from various sources. They have studied 182 cases of uterine rupture which occurred between 1950 and 1959 in the course of 79,162 deliveries (1 in 427 cases) in the Obstetric Unit of the University of Chile. There were 78 spontaneous ruptures (43 per cent) and 104 traumatic ruptures (57 per cent). These were treated as follows: Vaginal suture, 24 cases; Abdominal repair, 85 cases; Hysterectomy, 63 cases.

There were 18 maternal deaths (9·8 per cent) distributed thus: (1) Vaginal repair, 6 deaths (12·5 per cent); (2) Abdominal repair, 6 deaths (7·1 per cent); (3) Hysterectomy, 6 deaths (9·5 per cent).

Of the 85 patients who were treated by abdominal repair 30 were also sterilized. Of the 55 who were not sterilized, 16 were followed up. Of these 9 had already been delivered and one patient was 3 months pregnant. Of the 9 patients who had already been delivered, 5 had normal labours, 1 had a breech delivery, 1 suffered from a prolapse of the cord which was treated by internal version, 1 had a prophylactic Caesarean section, and 1 ruptured a previous Caesarean scar and was treated by laparotomy and repair with sterilization. The uterus was undamaged in all but the last case. There was no maternal death.

The authors make a plea for the wider use of conservative abdominal repair, which showed the lowest mortality (7·1 per cent) of any form of treatment employed in their series.

D. G. Wilson Clyne

79. **Recent Results in Cases of Ruptured Uterus.** (Neuere Resultate bei Uterusrupturen.)

By P. Bsteh. *Zbl. Gynäk.*, **82**, 1673–1679. Oct. 29, 1960. 2 tables. 12 refs.

The author reports that amongst 10,000 births occurring during the last 4 years there were 9 cases of ruptured uterus (0·09 per cent.) without any maternal death. Five children were lost, a mortality of 56 per cent. In 6 cases the rupture was spontaneous and in 3 traumatic. In 7 cases a deficiency of the uterine wall was either proved histologically or assumed on account of the previous history. Three cases followed one or more Caesarean sections, three occurred subsequent to curettage, in one case a suppurative myometritis could be demonstrated and in one an intramural fibromyoma. In two patients there was no known explanation for the occurrence of the rupture. The tears after Caesarean section were transverse, the others longitudinal.

The author considers that in order to assess the risk of rupture after Caesarean section one has to bear in mind that amongst the 10,000 births during the 4-year period there were 81 normal vaginal deliveries after Caesarean section.

In one patient the tear was repaired, but in the other 8 hysterectomy was carried out. The post-operative progress was free from any complication in all patients. The good results in the treatment of rupture of the uterus are largely attributed to good anaesthetic and blood transfusion services.

The author briefly discusses the problem of deciding whether a patient with a Caesarean scar should be allowed vaginal delivery. It is his practice to await rupture of the membrane. If the head engages with good pains within a short time, vaginal delivery is expected. If it fails to do so, section is carried out without further delay.

Bruce Eton

80. **The Physiological Basis of Obstetrical Anaesthesia with Pentothal.** (Bases physiologiques de l'anesthésie obstétricale au pentothal.)

By P. Guilhem, A. Pontonnier, R. Baux, P. Bennet, R. Pomarède and A. Finkeltin. *Gynéc. et Obstét.*, **59**, 301–321. 1960. 9 tables. 7 figs. 14 refs.

This French team, working in Toulouse, has investigated the physiological basis of the clinically observed fact that babies born to mothers fast asleep under

Pentothal anaesthesia, can be lively and cry actively at birth. They made 170 separate estimations of Pentothal concentrations: 103 in plasma, 27 in urine and 40 in tissues, mainly fat.

They described the technical details of their spectrophotometric method (adapted from Brodie's method) for determining absorption of Pentothal, and show that after a single intravenous injection of Pentothal into the mother, the strongest concentration of barbiturate reaches the brain in about 10 seconds. After about 20–25 seconds, Pentothal has completed its tour round the circulation and the concentration in the blood plasma of the mother starts to drop thereafter, so that within 2 minutes the level has dropped to one-fifth of what it was after 10 seconds.

On the other hand, because of some block between the mother and the baby, the baby's maximum level is not reached until after 2 minutes and it then starts dropping. It takes the best part of 20 seconds for any Pentothal to be found in the umbilical vein, and as the mother's level is dropping all the time the levels in the child are never very high, because the child's plasma Pentothal level only reaches that of the mother 2 minutes after her intravenous injection. In other words, it never receives a dose sufficient to put it to sleep, since the level after 2 minutes in the mother's blood would be insufficient to send *her* to sleep.

Tests done with repeated injections show that there is no cumulative effect either in the maternal or foetal blood streams so long as the injections are not repeated too rapidly.

These investigations were carried out in normal deliveries and at Caesarean section. At Caesarean section they took the opportunity of examining fat from the mother's abdominal wall for Pentothal levels. They also carried out experiments on one live anencephalic and one live hydrocephalic who died soon after delivery and also on a severely asphyxiated child who also died soon after delivery. They also investigated placental levels of Pentothal; and then drew diagrams to show the various blocks preventing high concentrations of Pentothal reaching the foetal circulation.

They come to the conclusion after many well thought out tests, that maternal fatty tissue and foetal liver tissue fix Pentothal and that the placenta acts as a temporary brake to the passage of Pentothal in the first 2 minutes when the concentration of the drug is highest in the mother's circulation. They believe that their findings indicate that Pentothal can be used much more freely than it is as an obstetric anaesthetic.

Elliot E. Philipp

PUERPERIUM

81. **Thrombectomy for Acute Iliofemoral Venous Thrombosis in the Postpartum Period.**

By J. A. HALLER, JR. *Surg. Gynec. Obstet.*, **112**, 75–81. Jan. 1961. 1 table. 6 figs. 6 refs.

The author discusses the results of thrombectomy in 5 cases of acute post-partum iliofemoral venous thrombosis. Operation was performed within 2–3 days of the onset of symptoms, under local anaesthesia, an S-shaped incision being made over the femoral canal commencing ½ inch below the inguinal fold. After isolation of the vessels, tapes were placed round the common, superficial and deep femoral veins. If a longitudinal incision into the common femoral vein revealed thrombus, the patient was given 50 milligrammes of heparin intravenously and the clot removed proximally and distally, usually by suction, the vein being closed with 5/0 silk.

After stating possible aetiological factors in post-partum venous thrombosis, the author points out that although pulmonary embolus does occur, it does so rarely, whereas the post-phlebitic limb is more common and poses a distressing problem. The gratifying results obtained both from immediate relief of pain and the absence of post-phlebitic limb changes lead the author to suggest that thrombectomy with anticoagulant therapy should be employed for this condition.

A. E. R. Buckle

82. **Postpartum Pre-eclampsia.**

By I. R. MCFADYEN. *Lancet*, **2**, 1009–1010. Nov. 5, 1960. 12 refs.

A case is described in which a patient developed post-partum pre-eclampsia following a post-partum eclamptic fit. There had been no evidence of ante-partum pre-eclampsia, but the patient did have a degree of hydramnios. Fifteen hours after delivery she had an eclamptic fit following which hypertension, oedema and albuminuria persisted for a further five days before subsiding gradually. The author describes three further cases of patients who developed signs of pre-eclampsia only after delivery and discusses the possible explanation. It is considered that the rise in 17-hydroxycorticosteroids known to occur immediately post-partum and to persist for several days may be responsible as the excess of pressor substance is no longer inactivated once the placenta has been delivered.

[No explanation is offered, however, as to why the phenomenon of post-partum pre-eclampsia seems to occur in only a very few patients since the sequence of events described presumably occurs in all.]

J. M. Brudenell

OBSTETRIC OPERATIONS

83. **The Place of the Vacuum Extractor in Operative Obstetrics.** (Zur Stellung des Vakuumextraktor in der operativen Geburtshilfe.)

By D. STERNBECK. *Zbl. Gynäk.*, **82**, 1427–1432. Sept. 10, 1960. 2 tables. 17 refs.

Although not a novel idea, the vacuum extractor (VE) which was reintroduced by Malmström is becoming increasingly popular. In a series of 153 cases the author found that the indications were very similar to those used for forceps delivery.

A particularly suitable indication is uterine inertia, which was treated more often by delivery with the VE than used to be the case when forceps was the only instrument available. In this type of case the VE proved to be more useful than oxytocic drugs and it seemed to be considerably less dangerous to mother and child than forceps.

The instrument can be used for immediate extraction of the child in urgent cases, but otherwise traction is only made during uterine contractions. This precaution reduces the traumatic effect of the instrument on the foetal head. The author considers that reported cases of necrosis, ulceration and subsequent alopecia are mainly produced by continuous traction. Intermittent traction is rarely necessary for longer than 20–30 minutes even if delivery is difficult. The instrument has sometimes been used when the cervix was not fully dilated.

As a result of the use of the VE the incidence of forceps operations was reduced from 1·92 to 0·87 per cent. The author concludes that the VE has now passed beyond the experimental stage and that it should form part of the regular practice of obstetric surgery.

Bruce Eton

84. **Non-union of Uterine Wounds.**

By A. H. BADAWAY. *Lancet*, **2**, 944–945. Oct. 29, 1960. 4 refs.

The author describes three cases of ruptured uterus in pregnancy. In two cases the rupture followed a previous lower segment Caesarean section and in one case a previous hysterotomy. He suggests that in the great majority of Caesarean scars which rupture in subsequent pregnancies there has been defective healing of the uterine wound following the original operaton so that only the peritoneal and subperitoneal layers unite, leaving a permanent defect in the muscle layer. When the patient becomes pregnant again the uterus distends and either during the pregnancy or in early labour rupture through the scar occurs. It would seem that the upper segment with its closely adherent peritoneal layer is more likely to give way during pregnancy. The loosely attached peritoneum of the utero-sacral fold in relation to the lower segment only becomes stretched during labour and is likely to remain intact until this time.

[There is as yet no very satisfactory way of assessing the integrity of a particular uterine scar with reference to its behaviour in a subsequent pregnancy. Routine hysterography after Caesarean section has been advocated both by Poidevin and Bockner (*J. Obstet. Gynaec. Brit. Emp.*, 1958, **65**, 278) and Baker (*Surg. Gynec. Obstet.*, 1955, **100**, 690) and may be helpful.]

J. M. Brudenell

85. **Hydroxydione (Presuren) as an Anaesthetic for Caesarean Section.** (Kaiserschnitt in Presurennarkose.)

By K. VARGA, K. MOROCZ and V. GYORVARI. *Geburtsh. u. Frauenheilk.*, **20**, 1255–1264. Nov. 1960. 4 figs. 29 refs.

Hydroxydione was used as the anaesthetic in 31 patients undergoing Caesarean section. Atropine was given pre-operatively; anaesthesia was induced by the intravenous injection of 1·0–1·5 g. of 10 per cent hydroxydione in physiological saline. The authors noted the state of the infants at delivery. They found that there was no respiratory depression of the infants if they were delivered within 9 minutes or later than 22 minutes after the injection had been given. One of the babies died 10 hours after delivery; at post-mortem asphyxial changes were found. The authors conclude that hydroxydione crosses the placental barrier. The mothers tolerated the anaesthetic well, and it was found suitable for patients with cardiac disease. *Peter J. Huntingford*

INFANT

86. **Ante-natal Determination of Foetal Sex in Prevention of Hereditary Diseases.**

By P. RIIS and F. FUCHS. *Lancet*, **2**, 180–182. July 23, 1960. 23 refs.

In Denmark legal abortion may be granted if there is a close risk that the child will suffer from some severe hereditary disease. The authors describe 2 cases where a woman who was a haemophilia carrier became pregnant. In each case the mother was only prepared to continue with the pregnancy if it could be determined that the foetus was female (and therefore unaffected). A sample of liquor amnii was obtained from both women by abdominal paracentesis. Cytological examination of the fluid confirmed the presence of chromatin positive cells. Both the women subsequently gave birth to female children. One of these was stillborn, but there was no suggestion that this was connected with the uterine puncture four months previously. The authors conclude that antenatal determination of foetal sex is of value in avoiding severe sex linked hereditary diseases, where legal abortion can be performed on these grounds.

J. M. Brudenell

87. **The Morphogenesis of the Suprarenal Cortex.** (Considérations sur les facteurs hormonaux de la morphogénèse de la cortico-surrénale. A propos d'un monstre acardiaque.)

By M. LACOMME, H. TUCHMANN-EUPLESSIS, L. MERCIER-PAROT and A. QUILLET. *Gynéc. et Obstét.*, **59**, 161–172. 1960. 10 figs. 10 refs.

This interesting article describes studies made on an acardiac monster.

The authors are especially struck by the perfect differentiation of structure in the suprarenal glands in this monster, which they point out is so at variance with the atrophy found in anencephalics. The development of the gland would appear to require a foetal corticotrophic hormone. In anencephaly the foetal hypophysis, deprived of hypothalamic connexions, is unable to elaborate the hormone. The maternal hormone either cannot traverse the placental barrier, or is of different constitution from the foetal hormone. *Elliot E. Philipp*

88. **The Quality of the Human Semen in Relation to Perinatal Mortality.**

By M. Furuhjelm, B. Jonson, C.-G. Lagergren and L. Lindgren. *Acta obstet. gynec. scand.*, **39**, 499–505. 1960. 2 figs. 9 refs.

The semen of the father was examined in 101 cases of perinatal death of the foetus born at the Sabbatsberg Hospital, Stockholm, during the years 1954–1959. Control cases were the male partners of 97 previously sterile couples, all of whom had living children within 2 years after the seminal examination.

Among the cases of perinatal death the concentration of the spermatozoa was lower, and the percentage of morphologically abnormal cells was higher than in the control cases. Among the intra-partum deaths the concentration of spermatozoa was lower than in the appropriate control group, and among the post-partum deaths the number of abnormal spermatozoa was higher than in the control group, but there was no difference in either the concentration or the number of morphologically abnormal spermatozoa, in the group of ante-partum deaths.

There was no correlation between the quality and quantity of the spermatozoa on the one hand, and the incidence of prematurity, postmaturity and complications during delivery.

However, the authors feel that there is a connexion between the quality of the semen and perinatal death.

N. Alders

89. **Staphylococcal Pneumonia in the Neonatal Period.**

By R. L. Edwards and G. A. Gresham. *Lancet*, **2**, 1057–1058. Nov. 12, 1960. 3 tables. 1 ref.

The authors describe eight cases of fatal staphylococcal pneumonia in neonates. All the infants were premature and in six of them infection appears to have arisen as a result of inhalation of infected liquor. In the two remaining cases infection probably arose after delivery. Seven were delivered normally and one by Caesarean section. In one of the normal deliveries a surgical induction had been performed. The causal organism in every case was *Staphylococcus pyogenes* and in five cases the antibiotic resistance patterns were the same as the indigenous hospital staphylococcus. The route of the infection in most cases seemed to be vaginal. In the infant the clinical course was often rapid. A wide range of histological appearances was found in the lungs, but in every case the infecting organism was isolated. The authors stress the continuing need for the diligent application of aseptic methods in the conduct of labour and the care of the newborn.

J. M. Brudenell

90. **Acquisition of Staphylococci by Newborns: Direct versus Indirect Transmission.**

By E. Wolinsky, P. J. Lipsitz, E. A. Mortimer, Jr. and C. H. Rammelkamp, Jr. *Lancet*, **2**, 620–622. Sept. 17, 1960.

The authors investigated the spread of staphylococci from a known nasal carrier infant to other infants in a special closed nursery set aside for the purpose. The uninfected infants were placed at varying distances from the carrier and the acquisition of staphylococci by them observed by means of repeated nasal and umbilical swabs. It was found that there was a low rate of spread from infant to infant by indirect (airborne droplet nuclei or dust) transmission. In contrast, however, a high proportion of the infants acquired organisms of bacteriophage type identical with those carried by two of the special nursing staff. It emerged as a result of further study that this spread is predominantly from the hands of the carrier to the infant, direct (heavy droplet) spread being again more important than the indirect route. Further investigations are being carried out in the department of paediatrics at Western Reserve University School of Medicine in Ohio to see how dissemination of organisms from personnel to infant can be interrupted.

J. M. Brudenell

GYNAECOLOGY

DISORDERS OF FUNCTION

91. **Comparative Studies of Oestrogen Levels in the Blood and Urine During the Menstrual Cycle.** (Vergleichende Untersuchungen über den Ostrogenspiegel im Blut und die Östrogenausscheidung im Harn während des Menstruationszyklus.)

By G. Ittrich. *Zbl. Gynäk.*, **82**, 1732–1734. Nov. 5, 1960. 2 figs. 3 refs.

The oestrogen and pregnanediol excretion in the urine and the oestrogen concentration in the blood were studied throughout a menstrual cycle. The excretion curves and the blood levels of oestrogens run a parallel course. The first peak in the blood level appears one day before the urinary excretion peak (ovulation peak).

From the author's summary

92. **The Use of Vitamin A in Pre-Menstrual Tension.**

By E. Block. *Acta obstet. gynec. scand.*, **39**, 586–592. 1960. 4 figs. 12 refs.

Two hundred and eighteen patients suffering from pre-menstrual tension were treated with 200,000 to 300,000 I.U. of vitamin A daily (4 to 6 tablets Arovit, La Roche) during the period when the symptoms were usually experienced. Although the author realizes that caution is necessary in the evaluation of the effects of treatment, which is based entirely on the patient's reports, he places on record that 60 per cent of the patients so treated reported that their feeling of "tension" and their headaches had considerably improved; a further 30 per cent reported some improvement. No side-effects were noted.

N. Alders

93. **Symptoms and Syndromes related to the Menstrual Cycle, Dysmenorrhoea and related Conditions.** (Síntomas y síndromas en relación con el ciclo menstrual. Dismenorrea y alteraciones afines.)

By C. ZUCKERMAN. *Revista Espanola de Obstetricia y Ginecologia*, **19**, 1–15. Jan.–Feb.; 87–98. Mar.–Apr. 1960. 136 refs.

This article gives an exhaustive summary of some 70 opinions and theories put forward as an explanation for the cause of dysmenorrhoea. The author then discusses 3,000 case histories in which he found 45 cases of the intermenstrual syndrome (1·5 per cent); 320 cases of premenstrual tension (about 11 per cent) and 410 cases of menstrual dysmenorrhoea (13·5 per cent). The article concludes with an equally exhaustive survey of therapeutic procedures, and a synopsis of 27 headings.

Those who are specially interested in dysmenorrhoea and related symptoms, and who wish to make a detailed study of the world literature, may confidently be recommended to refer to the extensive bibliography of Professor Zuckermann's article. They will find that little, if anything, of value is missing. *D. G. Wilson Clyne*

94. **Relaxin.**

By K. HALL. *J. Reprod. and Fertil.*, **1**, 368–384. 1960. 135 refs.

In the introduction, relaxin is described as a hormone or hormone-complex produced during pregnancy in the ovaries or reproductive tracts of the females of many species. Mention is made of the first-known function of relaxin, namely its collaboration with oestrogen in pre-parturitional relaxation of the symphysis pubis and sacro-iliac joints. Subsequent investigations have shown, *inter alia*, activity which reduces uterine myometrial activity and cervical tension and recent work has shown that relaxin can affect connective tissues in non-genital sites.

After detailing the methods of assay and species variations, the methods of preparation, biochemistry and pharmacology are discussed, it being stated that the structure of relaxin, whilst not finally elucidated, is thought to be a protein or polypeptide of low molecular weight.

The effects of relaxin on the relaxation of pelvic joints, inhibition of uterine myometrial activity, reduction in cervical tension, together with the effect on weight, water content and biochemical composition of the uterus, are mentioned. Its role in pregnancy and parturition and its effect on the mammary gland are also discussed. Most of the detailed work has been done on experimental animals, but reference is made to the results obtained in the human female.

Clinically, relaxin has been used in dysmenorrhoea where, although good results have been obtained, trials appear to have been inadequately controlled. Its use is also suggested, as an adjunct to oxytocin, in elective induction of labour at term. Results obtained in arresting premature labour have been equivocal. Finally, the use of relaxin with oestrogens in scleroderma and peripheral vascular disorders is mentioned.

In conclusion, it is emphasized that proper clinical trials of relaxin will be handicapped until the assay problem is solved and the nature of the active substance elucidated.

[This is a full review of available information, with an extensive list of references. Relaxin has been used for some years in America, but has received much less attention in this country.] *A. E. R. Buckle*

95. **Treatment of Prolonged Bleeding due to Menstrual Disorders with Minimal Doses of "Primolut N" and Ethinyl-nor-testosterone-acetate, Without the Use of Oestrogens.** (Östrogenfreie Behandlung der durch Zyklusfunktionsstörungen bedingten Dauerblutungen mit Mindestdosen von Primolut-N und Äthinyl-nor-testosteron-azetat.)

By G. WASCHKE. *Zbl. Gynäk.*, **82**, 1721-1732. Nov. 5, 1960. 1 table. 11 figs. 28 refs.

By means of 17-ethinyl-19-nor-testosterone ("Primolut N") in cases of menorrhagia haemostasis can be achieved within 24–72 hours and the bleeding can be reduced to normal amounts, comparable to normal menstruation. In the experience of the author 10 mg. of Primolut N or 2 mg. of ethinyl-nor-testosterone acetate daily constitute adequate doses for such treatment. Oestrogens do not seem to be required for the control of bleeding.

In a review of 158 cases of prolonged bleeding in which the endometrium was examined, proliferative changes were observed in 44, hyperplastic endometrium in 75, secretory endometrium in 9, hyperplastic proliferative and partly secretory in 3, a residue of hyperplastic endometrium in 10, basal layer only in 8, endometrial debris in 8 and regressive changes in one patient.

Whenever hormonal treatment failed there was an organic cause such as pregnancy or neoplasm. From this observation the author concludes that the efficiency of Primolut N in the control of functional uterine haemorrhage is such as to be of diagnostic value. He believes that these synthetic progestogens primarily act on the blood vessels in the functional and basal layers of the endometrium and possibly the uterine musculature.

Treatment with nor-testosterone is particularly suitable in girls suffering from juvenile menorrhagia in whom curettage should be avoided. In older women preliminary examination under anaesthesia and exploration of the uterus should be the rule before resorting to endocrine therapy. *Bruce Eton*

96. **Menorrhagia Due to Chronic Iron Deficiency.**

By M. L. TAYLOR, S. H. STURGIS, W. T. GOODALE and D. ASHBAUGH. *Obstet. and Gynec.*, **16**, 571–576. Nov. 1960. 4 tables. 10 refs.

In this report on 21 cases of menorrhagia, the authors believe that their results lend support to the long held thesis that anaemia itself may be a cause as well as a result of excessive menstrual flow. They show that a chronic iron deficiency can exist with a relatively normal haemoglobin level; serum iron estimation is a much more accurate way of diagnosing iron deficiency.

In most cases oral iron was sufficient to improve the menorrhagia; sometimes intramuscular iron was necessary. But if the menorrhagia did not improve with such measures it was usually found to be because of an organic or haematological disease. *J. G. Dumoulin*

97. **The Stein-Leventhal Syndrome.** (La sindrome di Stein Leventhal.)

By A. Bompiani and G. Mattioli. *Ann. Ostet. Ginec.*, **82**, 959. Sept. 1960. 61 figs. 127 refs.

This is a very long and detailed review of the Stein-Leventhal syndrome with a review of 23 cases and some discussion of the general aspects of virilism in women.

The following are the main conclusions. The ovarian lesion is a progressive one with continued sclerosis of the ovarian connective tissue and resulting amenorrhoea or oligomenorrhoea. The hypertrophy of the thecal apparatus of the ovary is irreversible. In very early cases the ovarian lesion may respond to gonadotrophin or to prednisone. There is a frequent association with lesions of uncertain origin and not necessarily related to the ovary such as hirsutism and obesity. A good therapeutic effect is obtained by resection of the ovaries at least as regards the restoration of ovarian function.

The authors believe that the basic lesion is in the pituitary with an imbalance of FSH and LH and associated ovarian and adrenal cortical disturbance.

Josephine Barnes

98. **A Clinical Study of the Androgenic Activity of a New Derivative of Testosterone: the Hexylenolic Ester and Methyl Testosterone Administered Orally.** (Studio clinico dell'attivita androgena di un nuovo derivato del testosterone: l'etere esilenolico del metil-testosterone somministrato per via orale.)

By L. Bartolotti and A. Bertaglia. *Ann. Ostet. Ginec.*, **82**, 939. Sept. 1960. 15 figs. 27 refs.

This new synthetic androgen is given by the oral route in capsules in oily solution. It has been used in 49 patients with conditions which usually respond to androgen therapy. The capsules contained 10 to 25 mg. and treatment was continued from 10 days to 3 months.

Good results were obtained in patients suffering from endocrine disorder. In cases with physical disease or anatomical changes the results were less good.

It is claimed that this new product gives a very reliable and constant androgenic effect with the undoubted advantages of oral administration. *Josephine Barnes*

INFECTIONS OF THE REPRODUCTIVE ORGANS

99. **Treatment of Urogenital Trichomoniasis with "Bayer 5360" (Flagyl) in Men and Women.** (Zur Behandlung der urogenitalen Trichomoniasis bei Männern und Frauen mit "Bayer 5360" (Flagyl).)

By H. Bauer. *Zbl. Gynäk.*, **82**, 1625–1631. Oct. 15, 1960. 2 tables. 12 refs.

The author reports on the result of treatment of 15 men. In 14 the trichomonas infection was demonstrated in the urethra, in 9 after prostatic massage. 250 mg. of "Flagyl" was given orally twice daily for 10 days. Follow-up examination showed bacteriological cure without any relapses in all cases.

Fifteen women were given oral and vaginal treatment for 12 days. In 13 of these the infection had been running a chronic course for up to 13 years. The cure rate was 100 per cent, but the follow-up examination in 5 of them was carried out after 1–4 weeks.

Eight of the patients were married or had partners, and in these cases both were treated at the same time. Gastro-intestinal side-effects were slight.

The main advantage of this treatment appears to be its efficiency, the short course of treatment required, its usefulness in the treatment of urinary infection, the possibility of treating husband and wife at the same time, the absence of subsequent vaginal mycosis and of manifestations of sensitization and the scantiness of side-effects. *Bruce Eton*

100. **Locan Pessaries in the Treatment of Trichomonal Vaginitis.**

By J. H. Eckersley, E. M. C. Dunlop and R. D. Catterall. *Lancet*, **2**, 526. Sept. 3, 1960. 1 table. 1 ref.

Locan pessaries containing amethocaine gr. 1/6, amylocaine gr. 1/12, solution of benzalkonium chloride 1/3 minim, lactic acid gr. ¼ and lactose gr. 4 in a non-staining oil-free base were used in the treatment of 63 cases of trichomonal vaginitis. The treatment was given for a maximum of 14 days and the results obtained compared with a similar series treated for the same length of time with acetarsol pessaries. No significant difference was found in the cure rate of the two series, but 5 of the locan patients developed sensitivity reactions. There were no sensitivity reactions to acetarsol. The authors conclude that locan should be used with caution, if at all. *J. M. Brudenell*

101. **Trichomoniasis and Its Relation to Cervical Atypia and Epidermoid Carcinoma of the Cervix.**

By T. A. Slate, J. W. Merritt and C. R. Kennedy. *West. J. Surg. Obstet. Gynec.*, **68**, 298–303. Sept.–Oct. 1960. 2 refs.

Over 15,000 cervical smears were examined to see if the presence of trichomonads caused atypical cytology which might be confused with carcinoma *in situ*. The incidence of trichomoniasis varied between 9 and 16 per cent in different groups of patients and the authors conclude that there are no pathognomonic cytological changes characteristic of the infection, and that evidence of perinuclear halo, hyperchromasia and dyskaryosis should be regarded as seriously in infected patients as in those without trichomonads. *D. C. A. Bevis*

102. **Treatment of Vaginal Candidiasis.**

By E. A. Nathanson. *Obstet. and Gynec.*, **16**, 601–604. Nov. 1960. 5 refs.

Uniformly good results were obtained in treating 100 cases of monilia vaginitis with Sporostacin cream—an odourless, white cream, containing 1 per cent chlordantoin. Five ml. of cream were inserted twice a day for 14 days: sometimes a second course was necessary. Sensitivity to the treatment was practically non-existent.

J. G. Dumoulin

103. **Prophylaxis and Treatment of Vaginitis and Proctitis due to Radium.** (Profilassi e terapia delle vagino-proctiti da radium.)

By G. TRONCONI. *Ann. Ostet. Ginec.*, **82**, 1026. Sept. 1960. 15 refs.

The author describes the well-known effects on the vagina and rectum of radium used for the treatment of advanced cancer of the cervix.

In a study of 18 such cases it was found that the local application of prednisone gave excellent results, including regression of vaginal hyperaemia. Local treatment with cortisone derivatives is therefore recommended in these cases.

Josephine Barnes

104. **Iontophoresis with Ronidase and Lipase in Chronic Inflammatory Conditions of the Genital Tract.** (Ionoforeza cu Ronidoza so Lidoza in afectiunile cronice inflamotoase. Al uteruli anexelor so tesutului celular parametrial.)

By I. N. REMBEZ. *Obstet. si Ginec.*, pp. 403–408. Sept. 1960. 14 refs.

This work describes iontophoresis with hyaluronidase in cases of chronic pelvic infection. Hyaluronidase increases the permeability of the tissues even in solutions as weak as 1 : 1,000,000. The author has elaborated a method of administration of this drug to the tissues with the aid of the galvanic current. The drugs he has used are Ronidase and Lipase, which are of Russian origin.

He sprinkles one of these substances on the abdominal wall and covers it with a flannel which has been soaked in saline and connected to one electrode. The other electrode is applied to a cushion soaked in saline and placed under the sacrum. The drug can also be placed in the vaginal fornices, so as to be nearer to the inflammatory site.

The author has treated 120 cases, all of which had previously been treated with various methods, without success. The ages of the patients ranged between 25 and 35 years. There were 34 nulliparae, but all of these had had miscarriages. The length of time that they had been suffering from the disease was between 3 and 8 years. In 96 cases chronic adnexitis was diagnosed, in 16 bilateral adnexitis and endometriosis, and in 8 parametritis. After the first few sessions of treatment there was a great improvement in both symptoms and physical signs. Two patients became pregnant, and a complete cure was obtained in 76 cases. The rest improved considerably. There was no recurrence in any of the cases treated.

Sylvia Lerer

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

105. **New Protective Measures in the Use of Radium.** (Neue Strahlenschutzmassnahmen in der Radiumtherapie.)

By F. STÄHLER and G. SCHENK. *Geburtsh. u. Frauenheilk.*, **20**, 1235–1242. Nov. 1960. 3 figs. 3 refs.

A special room has been used in the gynaecological department of the Jung-Stilling Hospital, Siegen, for the radium treatment of gynaecological cancer. The room is specially protected and equipped to prevent the scatter of irradiation. It contains a radium safe and a screened work-bench. The same room also serves as the place of radium insertion; the patient remains in the room until the radium is removed and replaced in the safe. A labour bed with a detachable foot and lithotomy attachments is used for the insertion of the radium, and the patient remains on it until she leaves the radium-room. At the side of the bed is a movable lead screen, which prevents the scatter of irradiation whilst the radium is *in situ*. Using this arrangement the authors have made about 100 applications of radium in a year. They compared the amount of irradiation to which the staff were exposed during the year in which the room was used with the preceding year. They found that all members of the staff were exposed to considerably less irradiation.

Peter J. Huntingford

106. **The Topography and Genesis of Uterine Fibromyomata.** (Zur Topographie und formalen Genese der Uterusmyome.)

By G. HÖRMANN. *Geburtsh. u. Frauenheilk.*, **20**, 942–953. 7 figs. 16 refs.

The author presents evidence to support his hypothesis that uterine fibromyomata arise in parts of the uterus that are particularly liable to disturbance during its development. Macroscopic study of the site of fibromyomata shows that they most often arise in the sagittal mid-plane of the uterus, and not haphazardly from anywhere in the myometrium. They also arise, but less commonly, at the uterine cornua and at the sides of the cervix. The author believes that at these sites of embryological fusion, or where ligamentous tissue is inserted into muscle, hormonal imbalance prevents a proper equilibrium from being established during the process of development between the muscular and connective tissue elements of the uterus.

Peter J. Huntingford

107. **Carcinoma in situ and the Transitional Zone of the Cervix Uteri.**

By C. F. FLUHMANN. *Obstet. and Gynec.*, **16**, 424–437. Oct. 1960. 15 figs. 34 refs.

In a previous study the author showed that between the squamous epithelium of the cervix and the columnar epithelium of the cervical canal there is an intervening area of immature cells, a transitional zone. In this study of 50 cases of carcinoma-*in-situ* of the cervix the distribution of the lesions showed that 36 involved either or both the transitional zone and the cervical canal and 14 extended over the portio. Seventeen were limited to the transitional zone, 4 to the canal, and only 2 to the portio. It is probable that lesions of the portio most often represent a later stage of a process that begins in the transitional zone or the canal.

On microscopic examination it was possible to discern varying degrees of differentiation which were grouped into 3 categories; in 34 cases the lesions were mixed.

The author suggests that squamous carcinoma-*in-situ* may arise either from the squamous, or more frequently, from the columnar epithelium of the cervix. In the latter case the immature cell involved corresponds to the subcolumnar cell, which normally forms the basis for the development of squamous prosoplasia, and is probably derived directly from columnar cells.

J. G. Dumoulin

108. **Early Diagnosis and Treatment of So-Called Pre-invasive Carcinoma of the Cervix.** (Zur Frage der Früherkennung und Behandlung des sog.präinvasiven Carcinom des Collum uteri.)

By E. KOFLER and H. KREMER. *Arch. Gynäk.*, **194**, 223–234. 1960. 5 tables. 1 illus. 41 refs.

Early diagnosis of cancer of the cervix has been facilitated by the introduction of colposcopy by Hinselmann in 1924, of cytology by Papanicolaou in 1928 and of colpomicroscopy by Antoine and Grünberger in 1949. All three methods have been used routinely in the First Gynaecological Clinic of Vienna during the last 8 years. The object of this paper is a critical comparison of the merits and faults inherent in these three diagnostic aids.

One hundred and fifteen women with a histological diagnosis of pre-invasive carcinoma of the cervix were studied between 1950–1958. The diagnosis was made by serial sectioning of the amputated cervix or cone biopsies. The age distribution of these patients varied between 30 and 75 years, the majority of patients (79 per cent) being under 50. Fifty-nine of these 115 patients had no symptoms suggestive of cancer and only about 25 per cent gave a "suspicious" history. On speculum examination only 9 had positive findings, 55 (48 per cent) appeared doubtful and 51 (44 per cent) completely normal. On colposcopic examination 46 women (40 per cent) were regarded as positive, 54 (47 per cent) as doubtful and 15 (13 per cent) as negative. Using the colpomicroscope 82 patients (71 per cent) were classified as positive, 19 (17 per cent) as doubtful and 14 (12 per cent) as negative. Cytology gave the highest diagnostic accuracy yielding 97 (84 per cent) positive and 11 (10 per cent) suspicious reports and only 7 (6 per cent) false negative findings. It would appear from these figures that, since cytology had the highest diagnostic accuracy, the use of the other two methods was superfluous. However, there was a good deal of overlapping, e.g. 6 of the 7 cytologically negative cases had positive or doubtful colposcopy or colpomicroscopy findings and only in one case all three investigations proved negative.

Of these 115 patients 27 had no clinical indication of malignant disease and were detected by the use of the special investigations. Twenty-three of these had positive smears and 1 had a "suspicious" report, 19 had positive and 2 doubtful colpomicroscopy findings and 5 women were found to have positive and 13 doubtful colposcopy reports.

The trends in the treatment of pre-invasive carcinoma have changed considerably between 1950 and 1958. Whereas the tendency in the first 4 years was towards a more radical approach (hysterectomy, Wertheim's hysterectomy or full radiotherapy) the following 4 years showed a remarkable restriction of therapy to conization and amputation of the cervix. Only in a few cases where histological examination of the amputated cervix proved that dissection had been carried out through atypical epithelium, simple hysterectomy was performed subsequently. In 3 patients with intact pregnancy at the time of diagnosis treatment was confined to small biopsies at the colposcopically determined sites of most pronounced epithelial atypia and the pregnancies allowed to continue. Following delivery conization or amputation of the cervix were carried out and the diagnosis histologically verified. Results of this therapeutic approach are not yet available since the observation period is not yet long enough.

Erica Wachtel

109. **Rapid Identification of Malignant Cells in Vaginal Smears by Cytoplasmic Fluorescence.**

By F. R. ELEVITCH and J. G. BRUNSON. *Surg. Gynec. Obstet.*, **112**, 3–10. Jan. 1961. 1 table. 12 figs. 8 refs.

Acridine orange is a fluorescent dye which has an affinity for both nucleic acids, but particularly RNA, an increased amount of which is found in actively proliferating cells such as those in embryonic or malignant tissue. The cell cytoplasm fluoresces green, orange or intense red-orange, depending on the concentration of RNA present. The authors discuss the use of acridine orange in the identification of malignant cells from cervical scrapings and vaginal smears, with particular reference to the number identifiable by red-orange fluorescence alone without the use of conventional morphological criteria of malignancy.

Having described the method of collection and the staining and microscopical technique, the results are given of 864 acridine orange stained smears from 641 unselected cases. A positive result was recorded where the cytoplasm of several cells fluoresced an intense red-orange. In the series, 7 out of 12 malignant tumours were identified by characteristic fluorescence alone, although all 12 were correctly identified by Papanicolaou smears.

Advantages claimed for this method of staining are that a polychromatic picture is obtained with a single dye, that the screening time is short, that malignant cells are easily identified and that it is comparatively easy to convert standard laboratory microscopes for use with this technique.

The limitation of acridine orange fluorescence is that increased RNA is found only in immature rapidly dividing cells in cervical squamous carcinoma and that slower-growing tumours, having less RNA than normal, may give a negative result. Poor results were also obtained by this technique in the case of smears from post-irradiated patients and it was felt that the method was of no value for the screening of these cases.

A. E. R. Buckle

110. **Viral Inclusion Bodies in Vaginal Smears.**
By A. VARGA and B. BROWELL. *Obstet. and Gynec.*, **16**, 441–444. Oct. 1960. 2 figs. 12 refs.

Cytoplasmic and nuclear inclusion bodies of many viruses are formed from viral particles. Although they generally indicate a virus infection, they have been identified in apparently healthy tissues and in diseases not caused by viruses. The lower genital tract and the vulva are host to a wide variety of viruses which may produce cytoplasmic or nuclear inclusion bodies. It is important to recognize this fact, so as not to confuse the nuclear inclusion bodies with atypical cells in Papanicolaou smears. Viruses can alter nuclear structure and may account for some instances of false positive Papanicolaou smears.

J. G. Dumoulin

111. **Postmortem Findings in Cancer of the Cervix: An Analysis of 108 Autopsies in the Past 5 Years.**
By L. S. J. SOTTO, J. B. GRAHAM and J. W. PICKREN. *Amer. J. Obstet. Gynec.*, **80**, 791–794. Oct. 1960. 7 tables. 3 refs.

A complete autopsy was done on 108 consecutive women who had been treated for cancer of the cervix. Eighty-five per cent had been treated within the last 5 years, and the rest 6 to 10 years before death. About 90 per cent had received what is now considered adequate primary treatment, the great majority by radiotherapy. In 50 per cent the cancer was in stages 1 or 2. Renal causes, manifested by uraemia, ureteral obstruction, hydronephrosis or pyelonephritis were the case of death in 37 per cent; peritonitis 11 per cent and respiratory failure 10 per cent were the other major causes of death. In 93 cases there was persistent cancer either in the pelvis or in distant metastases. The pelvic lymph nodes were involved in 28 women and the extra pelvic nodes in 55. Of the latter peri-aortic nodes were involved in 37, peribronchial in 20 and supraclavicular nodes in 12. There were 15 women who had no evidence of cancer at postmortem examination and who therefore had died from other causes. When cancer was present it was limited to the pelvis in only 15 per cent. Of these pelvic exenteration could have possibly eliminated the cancer in 11 patients—a maximum resectability of 13 per cent.

F. J. Browne

112. **The Results of Treatment of Carcinoma of the Cervix from 1949 to 1953.** (Behandlungsergebnisse beim Carcinoma colli uteri aus den Jahren 1949–1953.)
By W. BICKENBACH, J. RIES and J. BREITNER. *Geburtsh. u. Frauenheilk.*, **20**, 918–925. Aug. 1960. 2 tables. 4 refs.

The results of treatment of invasive carcinoma of the cervix in the First University Gynaecological Clinic, Munich, from 1949 to 1953, are described. This hospital claims to treat more cases of carcinoma of the cervix than any other hospital in the world (about 500 new cases of carcinoma of the cervix are treated each year). Radiotherapy is the mainstay of treatment: most patients are given three insertions of 40–80 mg. of radium at intervals of 10–14 days, so that at each insertion about 2,000 mg./hours of radium are given. This is followed by irradiation of the parametrium with x-rays through two anterior and two posterior fields. The total dose to each parametrium is between 1,800–2,400 röntgen, depending on the stage of the growth.

From 1949 to 1953, 2,517 patients with histologically-proven, invasive carcinoma of the cervix were treated. The distribution of the cases was as follows: stage I, 17·3 per cent; stage II, 29·2 per cent; stage III, 50·3 per cent; and stage IV, 3·2 per cent. The absolute five-year cure rate for all the patients was 53·6 per cent. In stage I the absolute five-year cure rate was 79 per cent; in stage II, 67·5 per cent; in stage III, 40·5 per cent; and in stage IV there were no survivors. Only 1 per cent of the patients were treated by surgery, in most of whom there were special problems, such as carcinoma of the cervix associated with pregnancy, or radio-resistant tumours.

The authors believe that these results support their contention that radiotherapy is the best form of treatment for most patients with invasive carcinoma of the cervix, including those with stage I or stage II growths.

Peter J. Huntingford

113. **Delay in the Treatment of Carcinoma of the Cervix.** (Zur Verschleppung des Kollumkarzinom.)
By P. SEGSCHNEIDER and H. G. RIEDEN. *Zbl. Gynäk.*, **82**, 1449–1457. Sept. 17, 1960. 2 tables. 9 figs. 49 refs.

The intervals between the onset of symptoms and admission to hospital of 1,996 patients suffering from carcinoma of the cervix were classified into four groups: (1) Duration of symptoms up to 2 weeks; (2) 3–12 weeks; (3) 13–52 weeks; (4) over 12 months. The incidence of stage III and IV cancers rose in the order of the groups from 10·8 to 23·4, 31·2 and 42·5 per cent respectively. There was a statistically significant relationship between the duration of symptoms and the cure rate which applied to each stage of the cancer. However, even in patients whose symptoms only lasted 4 weeks, the incidence of stage III and IV cancers was 38·8 per cent.

Delay caused by the patient appeared to be greater in the younger age groups, perhaps owing to failure to appreciate the symptoms.

Delay caused by the medical attendant was also greater amongst the younger group of patients (31–50 years), possibly because of misinterpretation of abnormal bleeding before the menopause.

Delay caused by faulty organization is attributed partly to patients and doctors and partly to health insurance and transport regulations.

The authors recommend that practitioners should be mainly concerned with the early detection of carcinoma by means of Schiller's iodine test, cytology, and possibly colposcopy. Although the doctor may wish to prove the exact diagnosis, the delay caused in so doing would not serve the best interests of the patient.

Bruce Eton

114. Urologic Problems in Carcinoma of the Cervix.

By C. J. E. KICKHAM. *Surg. Gynec. Obstet.*, **112**, 27-32. Jan. 1961. 6 refs.

The author expresses his views on the assessment and management, from the urological point of view, of some 1,800 women with carcinoma of the cervix. Emphasis is laid on the evaluation of the urinary tract once a diagnosis of carcinoma of the cervix had been made, and it is pointed out that ulcerative lesions have the highest incidence of vesical invasion, whereas, the infiltrating types frequently lead to ureteral obstruction.

The earliest indication of bladder disturbance is the effect of extra-vesical pressure, shown on cystoscopy as an elevation of the proximal trigone and distal posterior wall, the mucosa being normal. Later, congestion, submucosal haemorrhages and oedema appear, and finally nodules or definite tumour may project into the bladder.

Radiation injuries may be acute, with frequency, urgency and haematuria, or late in onset. In the latter instance, the average time from irradiation to the onset of symptoms was 27 months, the injury being due to vascular changes which may vary from a mild endarteritis to ischaemic necrosis. In the bladder the pathognomonic picture is of a central slough with a zone of hyperaemia and oedema in the mid-line just above the trigone, although the picture may vary from hyperaemia to frank fistula. It is pointed out that the latter may result from disease rather than radiation. It is therefore advised that periodic bladder inspection be performed in order to review prognosis.

Ureteral involvement is a grave prognostic sign, the usual site of occlusion being 4–6 centimetres above the orifice. Obstruction may occur in the absence of parametrial spread, from oedema or the inflammatory process adjacent to the growth leading to ultimate compression of the ureter. It is stated that obstruction of the normal ureter following radiation is rare. Management depends on whether the obstruction results from the disease or the effects of treatment. If the former, an expectant attitude should be adopted. Nephrostomy may be required for the relief of pain, for renal sepsis or for renal failure. Nephrectomy may be required where there is a non-functioning kidney if the function of the other kidney is normal.

Neurogenic disturbances of bladder function following Wertheim's hysterectomy were managed, in the group under review, by the use of an indwelling Foley catheter for 6–8 weeks, the patient returning to hospital at the end of this time for removal of the catheter. If drainage was satisfactory no further treatment was instituted, but further drainage was instituted if there was a high residual urine. A further object of this prolonged drainage by catheter was to decrease fistula formation, as overdistension of the bladder may lead to disturbance of the ureter from its new bed on the pelvic floor.

Ureteral damage following radical surgery is discussed and mention made of the, usually, transient hydroureter and hydro-nephrosis which may follow operation. With regard to surgical treatment for the damaged ureter, it is inadvisable to use the distal ureter because of its loss of power of contractility and peristalsis; re-implantation into the bladder or ileal loop conduit is preferred.

In super-radical procedures, the wet colostomy with ureteric transplant 6–8 centimetres above the stoma was originally performed, but the method of choice over recent years has been sigmoid colostomy and ileal conduit.

A. E. R. Buckle

115. Lymphatic Studies Pertaining to Local Spread of Carcinoma of the Rectum in the Female.

By I. R. BLOCK and I. F. ENQUIST. *Surg. Gynec. Obstet.*, **112**, 41–46. Jan. 1961. 1 table. 7 figs. 11 refs.

Because of the high incidence of local recurrence below the peritoneal reflection, following excision of the rectum for carcinoma, the authors investigated the lymphatic pathways from the anal canal and rectum to the female genitalia. The method employed was the injection of the vital dye, direct sky blue, into the anal canal and rectum of patients prior to hysterectomy or abdomino-perineal excision of the rectum. The injections were made at varying levels, some 12 hours prior to operation, one or two ml. of dye being used. The 12-hour interval was chosen to avoid too distant spread of the dye.

It was concluded that for carcinoma of the anal canal the lymphatic drainage would indicate excision of the lower two-thirds of the vagina in addition to abdomino-perineal resection of the rectum, whilst for carcinoma of the lower part of the rectum the studies suggested that total hysterectomy and bilateral salpingo-oöphorectomy, excision of the broad ligaments and the posterior vaginal wall was required, in addition to the abdomino-perineal excision of the rectum. For carcinoma in the upper rectum and sigmoid, anterior resection appeared adequate.

A. E. R. Buckle

116. Clinical Aspects of Metastatic Ovarian Cancer of Extragenital Origin.

By H. JOHANSSON. *Acta obstet. gynec. scand.*, **39**, 681–697. 1960. 7 figs. 28 refs.

This is a study of 79 cases of metastatic ovarian cancer of extragenital origin for which complete data were available in the records of Radiumhemmet, Stockholm, dating from January 1, 1930 to March 31, 1959.

In 84 per cent of these cases the primary tumour was in the intestinal tract (in the stomach in 39 per cent, in the pelvic colon and rectum in 21 per cent, and in the appendix, the ascending, transverse and descending colon in 24 per cent), in 14 per cent in the breast, and in the remaining 2 per cent in the kidney and pancreas. Almost 18 per cent of the patients were aged 40 years or less when the ovarian cancer was diagnosed; of the remainder, nearly 37 per cent were between 41 and 50, and over 45 per cent over 50 years of age.

The time intervening between the operation on the primary tumour and the diagnosis or removal of the ovarian metastasis varied considerably. Out of the 11 patients suffering from carcinoma of the breast, in one the ovarian secondary was found one month before the

discovery of the primary growth, and the metastasis was discovered within 1 year of the operation on the breast in 1 patient, between 1 and 3 years in 4 women, between 3 and 5 years twice, and after 9 to 16 years in 3 cases.

In roughly half of the patients suffering from primary cancer in the gastro-intestinal tract which was operated on before discovery of the ovarian metastasis, the latter was found at a comparatively early stage, not more than 3 years after the operation; in the other half of the cases of primary cancer in the gastro-intestinal tract, the primary growth was diagnosed only some time (up to 6 months) after the appearance of clinical symptoms referable to the ovarian metastasis.

The prognosis in metastatic ovarian carcinoma is very poor. In the present series only 10 of the 79 patients are alive. Five have not been followed up for 2 years, 2 have been clinically free from symptoms for about 2 years, and the remaining 3 for more than 3 years.

The author strongly recommends that women aged 40 years and over who are suffering from primary carcinoma of the digestive tract should be operatively castrated prophylactically at the time of the removal of the primary tumour. Bilateral oöphorectomy should also be done in women over 40 years of age suffering from carcinoma of the breast. *N. Alders*

117. **Bowel Complications due to Intraperitoneal Radioactive Gold.**

By P. S. PUTZKI and L. C. VARDEN. *Obstet. and Gynec.*, **16**, 398–400. Oct. 1960. 7 refs.

Two cases are described of bowel complications following the insertion into the peritoneal cavity of radioactive gold as part of the treatment of ovarian carcinoma. The first case developed a plastic peritonitis with intestinal obstruction, and the second a purulent peritonitis due to intestinal perforations.

Radioactive gold treatment does not prolong the life of patients, although it does seem to relieve pain and control ascites in some cases. As the authors show, however, it can cause intestinal injury.

J. G. Dumoulin

OPERATIONS

118. **Post-operative Prophylactic Anticoagulants.**

By D. G. CHALMERS, J. MARKS, J. E. BOTTOMLEY and O. LLOYD. *Lancet*, **2**, 220–222. July 30, 1960. 3 tables. 13 refs.

In the years 1949 to 1953 inclusive there were 159 cases of venous thrombosis and 189 cases of pulmonary embolism in post-operative obstetric and gynaecological patients in the United Cambridge hospitals. It was noted that the highest incidence of thrombo-embolic phenomena occurred in patients undergoing: (1) major gynaecological procedures over the age of 40 years; (2) Caesarean section; (3) operative procedures for malignant disease at any age; (4) any major gynaecological or obstetric procedure irrespective of age when there was a previous history of thrombophlebitis. It was decided to administer prophylactic anticoagulants to all patients in these groups from the third to the tenth post-operative days. Phenindione ("Dindevan") was the anticoagulant used and it was given in doses sufficient to maintain the prothrombin concentration (Quick's one stage method) at 15–30 per cent. The treatment was continued after the tenth day if the patient was still confined to bed.

During the years 1954 to 1958 when this regime was in force the incidence of venous thrombosis fell to 24 cases and of pulmonary embolism to 8 cases. Two of the cases of pulmonary embolism were fatal, whereas there were 9 fatal cases in a corresponding period before the prophylactic use of anticoagulants. The majority of cases where thrombo-embolism happened in spite of prophylactic anticoagulants had either completed the course before the condition occurred or had prothrombin contents of over 30 per cent at the time.

In all 1,877 patients received prophylactic anticoagulant therapy. Fifty-seven developed bleeding as a complication. Only 10 of these were sufficiently severe to require blood transfusion and vitamin K.

The authors conclude that the reduction in thrombo-embolism amongst the selected groups of obstetric and gynaecological patients justifies the routine post-operative administration to them of prophylactic anticoagulant therapy. *J. M. Brudenell*

119. **Hydroxydione as an Anaesthetic Agent in Gynaecology and Obstetrics.** (Hydroxydion als Vollnarkotikum in der Gynäkologie und Geburtshilfe.)

By R. MARTIN, K.-H. HARRICHHAUSEN and K.-H. SPONER. *Geburtsh. u. Frauenheilk.*, **20**, 1242–1251. Nov. 1960. 2 figs. 11 refs.

The steroid anaesthetic hydroxydione (Presuren) was used for more than 500 gynaecological operations in patients between 14 and 84 years of age. Patients were given pethidine 100 mg., promethazine 50 mg., and chlorpromazine 25 mg. before operation. Anaesthesia was induced with 0·5–1·0 g. of 5 per cent. hydroxydione in 0·9 per cent normal saline intravenously. In a few cases as much as 2·0 g. of hydroxydione were used. The patients quickly fell asleep; a few woke again for a short while before they finally became unconscious. The operation could be begun in most cases within 5 to 8 minutes of the injection. No major complications occurred. In 11 per cent of patients relaxation was inadequate and a muscle relaxant was used in addition. The operations lasted between 10 and 84 minutes. Most of the patients could be roused in 1½ to 2 hours. The side-effects encountered were: respiratory depression in 3 cases; phlebitis at the site of injection in 25 patients; a minor degree of post-operative circulatory collapse in 79 patients, in most of whom, however, the shock was probably due to the operation. This anaesthetic agent was used for 40 Caesarean sections (37 abdominal, 3 vaginal); 4 of the babies required resuscitation, but all of the children survived.

The authors consider hydroxydione, for which they found no contra-indications, to be an ideal anaesthetic for gynaecological operations. *Peter J. Huntingford*

120. **Surgical Treatment of Cancer of the Vulva.** (Traitement chirurgical des cancers de la vulve.)

By M. Mousseau and J.-M. Van den Broucke. *Gynéc. et Obstét.*, **59**, 370–385. 1960. 7 figs. 51 refs.

The authors review shortly the history of the surgical treatment of cancer of the vulva. They accept broadly the argument that only extensive surgery will serve to eradicate the disease and give a reasonable cure rate.

They describe their operation, which is not dissimilar from that described for the first time in 1948 by Stanley Way. Modifications of Way's operation, however, are in the sacrifice of less skin and, for reasons explained in the text, the avoidance of cutting the inguinal ligaments. They perform a rather more extensive extraperitoneal exploration of the glands of the pelvis, of the iliac vessels and of the para-aortic glands than is usual in this country, but they select cases carefully, determining on the following criteria the extent of the operation:

Lesions localized to the vulva. Since these lesions are usually multicentric, total vulvectomy with bilateral superficial adeno-cellulectomy is indicated. If the glands removed from the inguinal ridges show any involvement on rapid histological examination in the theatre, they proceed to deeper lymph-adenectomy. By cellulectomy is implied under-cutting of the skin of the lower abdomen and of the Scarpa's triangles, leaving only sufficient tissue attached to the skin to keep it viable. By this means they are able to repair the denuded area by primary suture which for the most part holds.

They describe how they carry out a more extended operation where the lower part of the vagina is involved and a most extended operation where the anus and rectum are involved.

[The best feature of this article is the simple but very effective line drawings demonstrating the operation. The series is too small to justify quotation of the results. The bibliography is excellent.] *Elliot E. Philipp*

121. **Cervical Conization During Pregnancy.**

By J. H. Ferguson and G. C. Brown. *Surg. Gynec. Obstet.*, **111**, 603-606. Nov. 1960. 8 refs.

The report is based on 50 conizations performed on 49 patients between the ages of 16 and 43 years, the gestation period at the time of operation varying from 3 to 39 weeks. Stressing the advantages of prompt accurate diagnosis, the authors give as indications for conization, the discovery of intra-epithelial carcinoma of the cervix by punch biopsy or a positive cervical cytology report.

Twenty-six operations were performed because of a positive punch biopsy; 17 revealed pre-invasive carcinoma and 3 an invasive carcinoma present. Seven cases were performed because of a punch biopsy diagnosis of dysplasia; 4 showed intra-epithelial carcinoma. Six cases had a negative punch biopsy but positive cytological report; 1 only showed intra-epithelial carcinoma. The remaining 11 had a positive cytological report only. Of these, intra-epithelial carcinoma was found in 6 and invasive carcinoma in 2.

Operation was performed with local haemostatic infiltration of the cervix, bleeding points being cauterized. Blood loss exceeded 200 ml. in 5 cases. There was no maternal death, but one patient had a pulmonary embolus and subsequently aborted.

Eight of the 50 pregnancies did not produce a surviving foetus (4 were due probably to other causes) and 8 of the patients were undelivered at the time of report. Premature and immature infants totalled 12 cases, 11 of which survived. In view of the risk to the foetus, the authors advise evaluation of each case by weighing the advantages of accurate diagnosis during the pregnancy against postponement to a later date.

[The authors do not state from what number of patients this group was diagnosed so that the incidence is unknown.] *A. E. R. Buckle*

122. **Uterine Perforation as a Complication of Dilatation and Curettage and Its Management.**

By P. P. Deasy and G. V. Anderson. *West. J. Surg. Obstet. Gynec.*, **68**, 294–297. Sept.–Oct. 1960. 18 refs.

The authors, from the University of Southern California, review the general features of uterine perforation and report that between March 1957 and August 1959, 10 patients required laparotomy following curettage. During this period there were 60–65 curettages each week. They advocate conservative treatment unless untoward symptoms develop, and point out that curettage carries a definite risk and should not be undertaken without sufficient justification. *D. C. A. Bevis*

123. **Cornual Cauterization.**

By M. Suter. *Obstet. and Gynec.*, **16**, 628–631. Nov. 1960. 1 table. 5 figs. 4 refs.

The author presents a series of 22 cases in which intra-uterine cornual cauterization was carried out as a method of sterilization. A preliminary hysterosalpingogram was done to ascertain the size and shape of the uterus and 15 patients were checked afterwards with tubal insufflation, 7 with hysterosalpingogram. The latter was a better method of checking than the former.

Results showed that tubal obstruction was successful in only 65 per cent of cases. *J. G. Dumoulin*

124. **The Blood Supply of the Internal Female Reproductive Organs. The Operative Treatment of Tubal Sterility.** (Blutversorgung der inneren Geschlechtsorgane der Frau und die operativen Behandlungsmethoden der Tubensterilität.)

By W. P. Pitschuew. *Zbl. Gynäk.*, **82**, 1645–1654. Oct. 22, 1960. 6 figs. 1 table. 11 refs.

The author studied the blood supply of the internal female genitalia at autopsies carried out in 55 women between the ages of 18 and 45. As soon as possible after death the uterine blood vessels were injected with radio-opaque material and were studied by X-rays, preparation of stereoscopic pictures and dissection.

It was shown that the main supply to the uterus and uterine tube is provided by the uterine artery, whereas

the blood supply to the ovary is shared equally by the uterine and ovarian arteries.

In the vicinity of the uterus the uterine artery gives off the cervico-vaginal branch which supplies the cervix and the upper third of the vagina. The course of the blood vessels in the cervix is from without inwards and from above downwards, forming an arch with the vessels of the opposite side which is convex downwards. In the isthmus the blood vessels run straight across but in the corpus the arches are convex upwards. These findings indicate that incisions in the upper third of the corpus should follow the course of the vessels in order to reduce the number of blood vessels divided by the incision.

The tubal artery was present in all cases and is the main branch of the uterine artery. The branches to the round ligament arise either from the uterine artery or its ovarian or tubal branch. The tubal artery usually runs along the lower border of the tube and supplies its medial half. It rarely reached the ampullary end of the tube. The author describes an accessory tubal artery which arises from the uterine artery and was found in 34 cases. It supplies the lateral half of the tube.

Near the lateral pole of the ovary the ovarian artery supplies a tubal branch which anastomoses either with the tubal branch of the uterine artery or with the accessory tubal artery. Within the tubes the blood vessels run in segments at right angles to the longitudinal axis of the tube except in the fimbriae where they run longitudinally. The segmental branches of the tubal artery encircle the tube and give off about 5 to 6 branches.

As the result of these studies the author recommends that in cases of salpingostomatoplasty resection of the ampullary end of the tube should be made by incision at right angles to the tube and not by longitudinal section which would interfere with much of the blood supply of the part. Implantation of the tube should be made into the posterior part of the uterine corpus through a uterine incision convex upwards, where there is more generous blood supply than in the front.

[It is rare to see an article by a Russian author in the *Zentralblatt*.]

Bruce Eton

125. **Rational Ovarian Surgery.**

By K. T. MacFarlane. *Amer. J. Obstet. Gynec.*, **80**, 683–691. Oct. 1960. 25 refs.

Probably the majority of operators who do hysterectomy for benign disease practise routine bilateral prophylactic oöphorectomy after the age of 40 to 45 years. Others conserve all ovarian tissue that is possible, even in the post-menopausal patient. The reported increase of atherosclerosis and coronary heart disease in castrated women, as well as several studies that show continuation of ovarian function after hysterectomy and the menopause would seem to support this attitude. Certainly the possibility of the development of malignant disease in the retained ovaries is no longer a valid reason for their routine removal. A third group decide each case on its individual indications. This requires accuracy of diagnosis of gross pathology at the operating table, free use of bisection of what seems to be a normal ovary, careful examination of both adnexal areas, and a knowledge of the patient as an individual. If the ovary is being retained its blood supply must be conserved. The utero-ovarian anastomosis should be exposed. The round ligament and the broad ligament should be clamped and ligatured separately thus giving free access to the anterior side of the opened broad ligament. In this way it is possible to attach the medial end of the broad ligament to the lateral portion of the vault which preserves an almost normal position of the ovary and maintains its circulation without tension or constriction.

In chronic pelvic inflammation with salpingo-oöphoritis it is usually necessary to perform total hysterectomy with bilateral salpingo-oöphorectomy. Oöphorectomy in breast cancer is often undertaken by the author for palliation in the presence of metastatic disease, and in his hands has symptomatically improved 60 per cent of the patients. Of 19 cases during the last 2 years only 5 showed cortico-nodular stromal hyperplasia in the removed ovaries. Six showed atrophic ovaries, and 8 were pre-menopausal ovaries showing normal ovarian activity.

Unless carcinoma of the ovary is discovered early—often by accident, the end results from any therapy are most disappointing, and the author therefore advocates routine examination of all women admitted to hospital, or attending hospital clinics whether or not their symptoms are pelvic in type. The same applies to patients coming under the care of general practitioners who should have acquired the ability to do a comprehensive pelvic examination on the female patients.

F. J. Browne

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Sampson, P. (1940): *Obstetrics for Midwives*. 2nd edition. Fraser, London. p. 9.

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ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

THE Prime Minister of Australia, The Right Hon. Robert Gordon Menzies, visited the College in Sussex Place, Regent's Park, at 6 p.m. on 15th March, when he was admitted to the Honorary Fellowship of the College.

AT a Meeting of the Council held in the College on Saturday, 25th March, 1961, with the President, Mr. Arthur C. H. Bell, in the Chair, the gift of a further £6,000 from the Wellcome Trust for library purposes was gratefully acknowledged.